Neurocognitive networks for social cognition: Insights from diffusion weighted imaging and frontotemporal dementia

A thesis submitted for the degree of Doctor of Philosophy

By

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Thesis summary

Empathy is a complex and multicomponent social cognitive function. It is underpinned by large-scale neurocognitive networks, the precise cognitive and neural structure of which remains debated. Despite this, relatively little work has considered the cognitive or neural components of empathy at the network-level. Here I present work using diffusion weighted magnetic resonance imaging (DWI) in healthy adults, and cognitive and behavioural assessment in a relatively rare form of dementia, the behavioural variant of frontotemporal dementia (bvFTD). Using these methods I explore: (a) the relationship between the microstructural properties of white matter tracts that mediate connectivity between distinct neurocognitive networks and separable cognitive components of empathic cognition (b) the cognitive and behavioural consequences of perturbation to neurocognitive networks in dementia.

BvFTD is of interest here as it appears to preferentially target neural networks that support socioemotional processing. In chapters 2 and 3, evidence regarding the white matter structures that are affected by bvFTD guides investigations of the relationship between the microstructural properties of specific white matter tracts and social cognitive functioning in the healthy adult brain. In these chapters, I show that, in young healthy adults, two white matter pathways, sensitive to early changes in bvFTD, the Uncinate fasciculus (UF) and the cingulum bundle (CB), are related to individual differences in two components of empathic functioning, respectively: facial emotion decoding and mentalising. In chapter 4 I show the dissociation of performance on tasks assessing these cognitive functions in an individual with early bvFTD. I highlight the sensitivity and potential clinical utility of tasks assessing literary fiction-based mentalising. In Chapter 5 I present a detailed qualitative description of social cognitive change in frontotemporal dementia (FTD), from the perspective of family members. I consider what such detailed descriptions of everyday behaviour may tell us about the cognitive underpinnings of complex social behaviour.

The findings of this thesis further our understanding of the dissociable neurocognitive networks that support empathic functioning, including their structural underpinnings and the behavioural consequences of their perturbation. In the general discussion, I consider the implications of this work for our understanding of social cognitive functioning and bvFTD.

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Contents

Abbreviations

Abbreviation	Full Name
ACC	Anterior Cingulate Cortex
AD	Alzheimer's disease
ASD	Autism Spectrum Disorder
ATL	Anterior Temporal Lobe
BF	Bayes Factor
BVFTD	Behavioural variant of Frontotemporal Dementia
CB	Cingulum Bundle
CC	Corpus Callosum
CSD	Constrained Spherical Deconvolution
CST	Corticospinal Tract
CUBRIC	Cardiff University Brain Research Imaging Centre
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
FA	Fractional Anisotropy
FMRI	Functional Magnetic Resonance Imaging
FTD	Frontotemporal Dementia
FTLD	Frontotemporal Lobar degeneration
FUS	Fused in Sarcoma
GRN	Progranulin
HARDI	High Angular Resolution Diffusion Imaging
LH	Left Hemisphere
MAPT	Microtubule Associated Protein Tau
MPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
NMR	Nuclear Magnetic Resonance
OMPFC	Orbital and Medial Prefrontal Cortex
PAM	Perception Action Model
PCC	Posterior Cingulate Cortex

PNFA	Progressive Nonfluent Aphasia
RH	Right Hemisphere
RMET	Reading the Mind in the Eyes Task
ROI	Region of Interest
SD	Semantic Dementia
SPECT	Single-Photon Emission Computed Tomography
TASIT	The Awareness of Social Inference Test
TBSS	Tract-Based Spatial Statistics
TP	Temporal Pole
TPJ	Temporoparietal Junction
UF	Uncinate Fasciculus
VEN	Von-Economo Neuron
VMPFC	Ventromedial Prefrontal Cortex

1

Introduction

1.1 Social cognitive neuroscience: a brief introduction

Humans are a highly social species, and as such, a great deal of day-to-day human behaviour is underpinned by our ability to understand and interact effectively with others. Since the time of ancient Greece, such social behaviour has been proposed to rely upon the physical structure of the brain (Lieberman, 2007). Modern day social neuroscience is however frequently traced to the 19th Century and the famous case of Phineas Gage (Adolphs et al., 1999; Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994; Lieberman, 2007, 2012). Gage was a young railroad worker who underwent profound social changes when he sustained extensive brain damage when a tamping iron was blown through his frontal lobe (Damasio et al., 1994). Despite this long history of linking brain structure with social behaviour, until relatively recently, in modern psychology, social behaviour was principally the domain of the social psychologist (Allport, 1920; Bandura, Ross, & Ross, 1961; Cacioppo, Berntson, Sheridan, & McClintock, 2000; Lieberman, 2007; Milgram, 1963).

Social neuroscience is the term given to the study of the neural basis of social behaviour. Within the recent literature, social neuroscience can be traced back to the work of Leslie Brothers (Adolphs et al., 1999; Brothers, 1990; Frith, 2007; Lieberman, 2007). Brothers and others showed that in monkeys, lesions to regions such as the anterior temporal lobes (ATL) lead to blunted affect and reduced responsiveness to social communication (Brothers, 1990; Kling, 1986). Based on this work, in her seminal work in 1990, Brothers proposed that social behaviour may reasonably be believed to be supported by a specialised system of brain regions and that this system included the amygdala, orbitofrontal cortex and ATL (Brothers, 1990). Thanks to such evidence associating specific neural regions with social functioning arguments were made for the establishment of a field of social neuroscience (Cacioppo & Berntson, 1992; Cacioppo et al., 2000) (See Lieberman (2012) for a more in-depth historical overview).

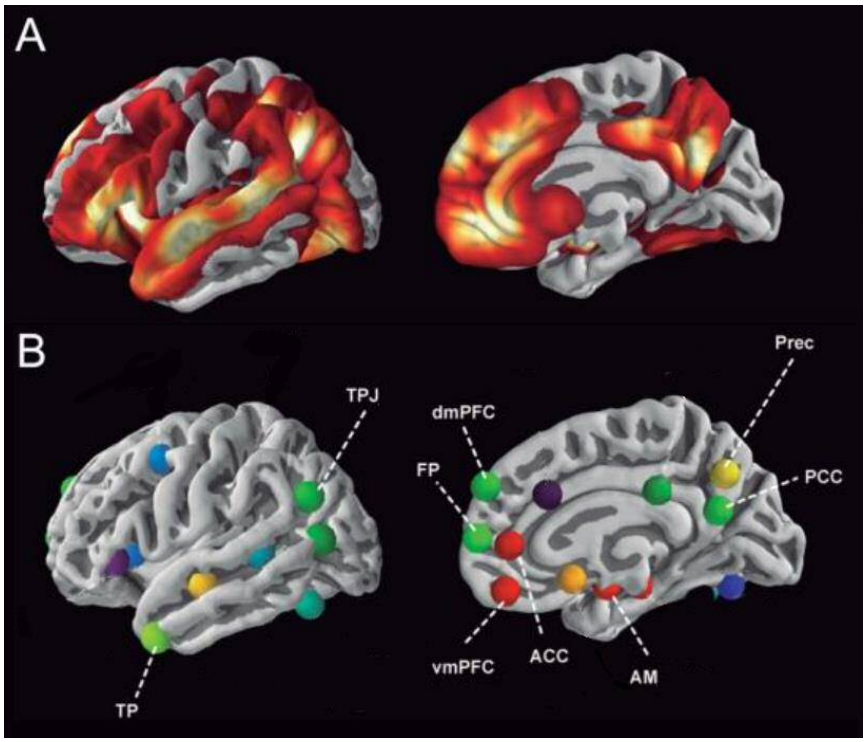

Figure 1.1 The social brain. (A) Functional activity probabilistic map from a meta-analysis of studies of social-affective processing. (B) Cortical regions identified as showing convergent activity across social-affective tasks. TP=Temporal Pole; TPJ=Temporoparietal junction; FP=Frontal Pole; dmPFC= dorsomedial prefrontal cortex; vmPFC= Ventromedial prefrontal cortex; ACC= Anterior cingulate cortex, AM=Amygdala; Prec=Precuneus; PCC= Posterior cingulate cortex. *Adapted from Alcala-Lopez et al. (2017)*

While early social neuroscience work focused on animal-based research, the development of the field of social neuroscience was human *in- vivo* research made possible by the advent of non-invasive brain imaging as this allowed for. Such in vivo human research has supported findings from animal work and shown the presence of a system of brain regions selectively involved in social cognition (Abu-Akel & Shamay-Tsoory, 2011; Adolphs, 2009; Bickart, Dickerson, & Feldman Barrett, 2014). Consistent with previous animal work, the social brain in humans was seen to include the amygdala and prefrontal cortex (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Adolphs et al., 1999; Beer, Heerey, Keltner, Scabini, & Knight, 2003; Hornak et al., 2003) (See figure 1.1). The use of neuroimaging methods additionally extended our understanding of the social brain by allowing social neuroscientists to study far more complex and nuanced social behaviours than those previously studied in non-human animals. Indeed, brain imaging allowed for the study of social behaviours that we cannot be certain even occur in non-human species, such as empathy or the attribution of mental states to ourselves and others (Saxe, 2006),

sometimes termed theory of mind or mentalising. Such abilities showed the involvement of brain regions, such as the temporo-parietal junction (TPJ), medial prefrontal cortex (mPFC) and anterior and posterior cingulate cortices (ACC, PCC) in complex human social cognitive functions such as mentalising (D'Argembeau et al., 2007; Hornak et al., 2003; Hughes & Beer, 2012; Saxe & Kanwisher, 2003; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). For an overview of cortical regions involved in social cognition, see Figure 1.1.

The emergence of neuroimaging enabled the study of not only of the neural basis of social behaviour at a gross level, but also the study of more specific cognitive components of social cognition (Lieberman, 2007; Ochsner & Lieberman, 2001; Stanley & Adolphs, 2013) by allowing for human *in-vivo* studies of the relationship between brain and behaviour. This level of analysis bridges social cognition and brain structure and allows for the consideration of neurocognitive networks that underlie social behaviour, giving rise to the field of social cognitive neuroscience (Lieberman, 2000; Ochsner & Lieberman, 2001; Ochsner & Schacter, 2012). Social cognitive neuroscience focuses on establishing the neural underpinnings of the specific cognitive processes that are critical for social behaviour. As it is intrinsically interdisciplinary, progress in social cognitive neuroscience can add to multiple domains of understanding, helping to develop theories of the cognitive structure of social behaviours and progressing our understanding of the functions (and dysfunctions) of specific neural systems (Ochsner & Lieberman, 2001).

Though social cognitive neuroscience was highlighted in a Nature Neuroscience editorial in 2012 as a relatively ignored domain of neuroscience ("Focus on social neuroscience," 2012), understanding of the neural basis of social cognition is of great clinical importance. Understanding the neural basis of specific cognitive components that underpin social behaviour may be key to understanding the prominent social behavioural alteration seen in many clinical conditions such as Autism spectrum disorder (ASD), Schizophrenia and Frontotemporal dementia (FTD) (Leekam, 2016; Rascovsky et al., 2011; Snowden et al., 2003). The social cognitive neuroscience approach may therefore help to develop our understanding of such conditions by elucidating the cognitive structure of social behaviours, the neural systems that support them, and how both may alter in disease. Social cognitive neuroscience has been posited to cover four broad domains: Understanding others, understanding the self, controlling the self, and the interface between the self and others, (e.g. decision making, attitudes) (Lieberman, 2007). From a clinical perspective, understanding others is a particularly important domain of social cognitive neuroscience as it appears to show alteration in many conditions characterised by altered social behaviour (Leekam,

2016; Rascovsky et al., 2011; Snowden et al., 2003). Empathy is one ability that is inextricably linked with the ability to understand others and which is prominently altered in several groups who show abnormal social behaviour (Baez et al., 2014; Blair, 2005; Brook & Kosson, 2013; Decety & Jackson, 2004; Harari, Shamay-Tsoory, Ravid, & Levkovitz, 2010; Rogers, Dziobek, Hassenstab, Wolf, & Convit, 2007; Trojsi et al., 2016; Wood & Williams, 2008). As such, empathy is an important research focus for the field of social cognitive neuroscience.

1.2 Empathy

1.2.1 The importance of empathy

"Empathy seems like a simple concept- one feels what another person feels – but the more one learns about it, the more complex it becomes"

Hoffman (1984)

A prominent question within social cognitive neuroscience that remains unanswered is: what are the neurocognitive underpinnings of empathy? Of the functions that may be described as social cognitive, few are more important than empathy as it is a cornerstone of human relationships and societies (Tomasello, 2014; Zaki & Ochsner, 2012). Empathy has however posed a considerable challenge both to define and to study. As stated by Hoffman, one of the pioneers of modern empathy research, empathy is a deceptively simple concept (Hoffman, 1984).

The capacity to understand the mental and emotional states of others and comprehend their desires and intentions is a key component of empathy, an ability which may have a key role in the development of pro-social behaviour (Farrant, Devine, Maybery, & Fletcher, 2012; Findlay, Girardi, & Coplan, 2006; Williams, O'Driscoll, & Moore, 2014). Indeed impairment in empathy is associated with the presence of prominent anti-social behaviour (Brook & Kosson, 2013; Yavuz, Şahin, Ulusoy, Ufuk Ipek, & Kurt, 2016). In the clinical domain, understanding empathy may have further importance, as altered empathic functioning has been discussed in relation to a range of clinical diagnoses, including Narcissistic personality disorder (Baskin-Sommers, Krusemark, & Ronningstam, 2014), Antisocial personality disorder (Yavuz et al., 2016) Schizophrenia (Shamay-

Tsoory & Aharon-Peretz, 2007) and the behavioural variant of FTD (bvFTD) (Rascovsky et al., 2011).

1.2.2 What is empathy?

Empathy is broadly the comprehension and sharing of the experiences of another, yet its definition is far from simple. The literature is replete with definitions of 'Empathy', indeed in one review it was noted that "there are probably nearly as many definitions of empathy as there are people working on the topic" (de Vignemont & Singer, 2006). Yet while definitions share a consistent central theme of the ability to understand the experiences of others, considerable differences exist between them (Batson, 2009). The challenge of defining empathy is partly a result of its multidisciplinary history, empathy research has a protracted history within philosophy as well as psychology, for example seminal work on empathy was produced by the 20th Century philosopher Edith Stein (Stein, 1989, 1993). Even within what may be considered psychology, researchers whose approaches could be considered to hail from very different branches of the field, such as cognitive, developmental, neuro and social psychology all work on empathy research (Batson, 2009; Chakrabarti & Baron-Cohen, 2006; Davis, 1983; Decety, 2010; Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004; Preston & de Waal, 2002; Singer, 2006; Walter, 2012). The different epistemologies and interests of these disciplines has, however, led to many definitions appearing within the literature.

Within the psychological literature a major distinction between definitions of empathy is based on the relative emphasis on the affect sharing component of empathy. In one school of thought empathy is argued to be present only if four criteria are met: (i) one is in an affective state; (ii) this state is isomorphic to another person's affective state; (iii) this state is elicited by the observation or imagination of another person's affective state; (iv) one knows that the other person is the source of one's own affective state (de Vignemont & Singer, 2006; Singer & Lamm, 2009). Here, sympathy, empathic concern and compassion are viewed as being distinct from empathy due to not involving affective sharing (Singer & Lamm, 2009). In an alternative view, empathy is seen as a wider phenomenon, not contingent upon shared emotion. Here, empathising is defined as the drive to understand the mental (including emotional) state of others. As such the focus of these definitions is far more on the prediction of the behaviour of others and the ability to respond

appropriately to it, rather than on emotion congruence *per se* (Chakrabarti & Baron-Cohen, 2006; Takeuchi et al., 2014).

Considering existing definitions of empathy, one issue with definitions that focus on affect sharing is that they define empathy based on its necessary outcome. While at a conceptual or experiential level this may make sense, at an experimental level this poses challenges, as it requires assessment of what a participant is feeling (discussed in more detail later). Considerations may therefore be better to focus on the cognitive processes underlying empathy rather than its outcome *per se* (Hoffman, 1984). This approach is consistent with the social cognitive neuroscience approach and a focus on the neural systems and the cognitive components that support complex functions. Consistent with a social cognitive neuroscience approach, it is now generally agreed that empathy is not a single construct, but may be best considered an umbrella term (de Waal & Preston, 2017), or a "Psychological construct which accounts for a superordinate category of behaviours" (Decety & Jackson, 2004). As such, it may be of little value to seek a single neural substrate for empathy or focus entirely on the outcome of behaviour. Instead definitions of empathy may necessarily involve a consideration of the neurocognitive systems that underpin empathic behaviour (Blair, 2008). Indeed, Jean Decety, an established researcher in the field, has suggested abandoning the use of the 'catchall' term 'empathy', and to instead use more precise terms (Decety & Cowell, 2014). This is entirely feasible within a social cognitive neuroscience approach, as while a social neuroscience or social psychological approach may necessitate the definition of empathy *a priori*. A social cognitive neuroscience approach can break empathy down into its constituent cognitive components and investigate the neural substrates of each (Decety & Jackson, 2004). This approach allows us to both explore the core cognitive processes underlying empathy and use findings from such work to inductively build models of neurocognitive systems which may not exclusively be involved in empathy but which may support empathic behaviour.

Consistent with the social cognitive neuroscience approach, this thesis will focus on the cognitive-affective processes necessary for empathy rather than focusing on specific experiences or outcome behaviours indicative of empathising. For the purposes of this thesis, "empathy" will not be considered to be a single cognitive function but instead to be a umbrella term that covers a range of cognitive processes that allow for the understanding of the emotional state of other individuals, in line with the proposal of Decety (Decety & Cowell, 2014). As a result of this definition, within this thesis, cognitive processes that may not encompass all aspects of empathic behaviour, but which may make up a wider network of processes that work together to facilitate

the understanding of the emotions of others will be considered. As such, in line with previous proposals (Chakrabarti & Baron-Cohen, 2006; Takeuchi et al., 2014), the sharing of emotional state will not be considered to be a necessary component of the cognitive processes relevant to empathy. Indeed, because of the methodological challenges of assessing shared emotion outlined above, the sharing of emotional state will not be considered in the consideration of empathy given here. Though these components in isolation may not be sufficient for many previous definitions of empathy, together they should be necessary for aspects of empathic behaviour.

1.2.3 Neurocognitive components of empathy

Models of empathic functioning that describe the neurocognitive components underpinning the ability to understand others tend to identify two primary systems. Indeed, there is a general consensus that empathy and the ability to understand others may best be thought of as comprising of two, to some extent separable systems, commonly termed cognitive and affective empathy (Davis, 1983; Decety, 2011; Decety & Jackson, 2004; Shamay-Tsoory, 2011; Shamay-Tsoory, Aharon-Peretz, & Perry, 2009; Zaki & Ochsner, 2012).

1.2.3.1 Affective empathy

Affective empathy can broadly be described as the understanding of the experiences of others based upon the perception of their expressive behaviour. Affective components of empathy have been argued to be a bottom-up process whereby the direct observation of others results in the sharing and understanding of their emotion (Decety & Lamm, 2006; Singer & Lamm, 2009).

Affective empathy has been conceptualised and divided in different ways by different researchers. Models of affective empathy are however intrinsically perceptual and give a central role to the perception of the expressive behaviour of others. As such they are conceived to be driven by perceptual input, consistent with evolutionarily based descriptions of empathy (Preston & de Waal, 2002). In the two-stream model of empathy proposed by Shamay-Tsoory (2011; 2009), affective empathy is described as a single domain underpinned by three principal components; emotional contagion, emotion recognition, and shared pain (see Figure 1.2). In a related model, proposed by Blair (2005), the same principal components are described but themselves split into two systems, emotional empathy (broadly emotion recognition) and motor empathy (involving

emotion contagion and shared pain). Here, these components will be discussed in the context of the latter, two way split; motor empathy and perceptual empathy.

1.2.3.1.1 Motor empathy

Motor empathy is the presence of motor synchrony between an observer and the target of their observation. It encompasses two of the process outlined as components of affective empathy in Shamay-Tsoory's two-stream model (Shamay-Tsoory, 2011): Emotion contagion, where the emotions of one individual spontaneously trigger the same emotions in another, and shared pain. Motor empathy, 'mirroring' or 'resonance' is considered a primitive form of empathy (Blair, 2005; Decety & Jackson, 2004). This is partly because apparent emotion contagion is seen in species other than humans. When exposed to others in distress, rats will display distress (Church, 1959; Masserman, Wechkin, & Terris, 1964) and act to free others from distressing restraints, even when it poses no direct benefit to themselves (Bartal, Decety, & Mason, 2011). Such apparent emotion sharing forms the basis of the neurobehavioral perception-action model (PAM) (de Waal & Preston, 2017; Preston & de Waal, 2002), in which empathy is proposed to be a relatively automatic and perceptual process whereby the perception of another's emotional state directly activates the corresponding emotional representations in the self ('state matching').

The concept of motor empathy is intertwined with the concept of mirror neurons, neurons that show similar activity when an action is performed by the self or observed being performed by another (Rizzolatti & Craighero, 2004). This system was originally described in non-human primates but following neuroimaging work showing evidence for a similar system in humans this has been translated to the notion of a fronto-parietal motor mirroring system in humans (Kilner, Friston, & Frith, 2007). This system is thought to contribute to the "direct" perception and understanding (or prediction) of actions, including emotionally expressive actions (Rizzolatti & Craighero, 2004; Kilner et al., 2007). In humans, research that has focused on motor mimicry, and automatic somatosensory representations of affective states, has tended to investigate the overlap in neural activity between direct experiences of pain and observations of others in pain. This is such a common approach that it has been claimed that the majority of studies that have investigated the neuropsychology of empathy have looked at pain (Singer & Lamm, 2009). Dubbed the 'pain network', regions that show activity in relation to both the first person experience and observation of others in pain include the insular and the mid cingulate cortex (de Vignemont & Singer, 2006; Lamm, Batson, & Decety, 2007; Lamm, Decety, & Singer, 2011; Singer et al., 2004).

Consistent with the 'pain network' having a role in empathy, activity within these regions varies in line with modulators of empathic feeling, such as liking for the other (Fox, Sobhani, & Aziz-Zadeh, 2013; Singer, 2006). Activity in these regions has also been claimed to be sensitive to the experience and observation of sensations other than pain, such as disgust (Jabbi, Swart, & Keysers, 2007; Wicker, Perrett, Baron-Cohen, & Decety, 2003). Yet, the involvement of these regions in empathy in general is questionable. These regions do not reliably show activity in response to states such as happiness, pleasure and stress (Morelli, Rameson, & Lieberman, 2014; Wicker et al., 2003). Instead, these regions may be better thought of as representing aversive experiences and form an 'aversion' (Bickart et al., 2014)(See figure 1.3) or 'salience' network (Menon, 2015) as they are responsive to a variety of aversive and salient experiences, such as unfairness (Corradi-Dell'Acqua, Tusche, Vuilleumier, & Singer, 2016). The representation of these regions as 'empathy regions' may simply be due to pain research's disproportionate representation in investigations of the neural underpinning of empathy (Bernhardt & Singer, 2012; Fan, Duncan, de Greck, & Northoff, 2011), rather than their key role in empathy *per se*.

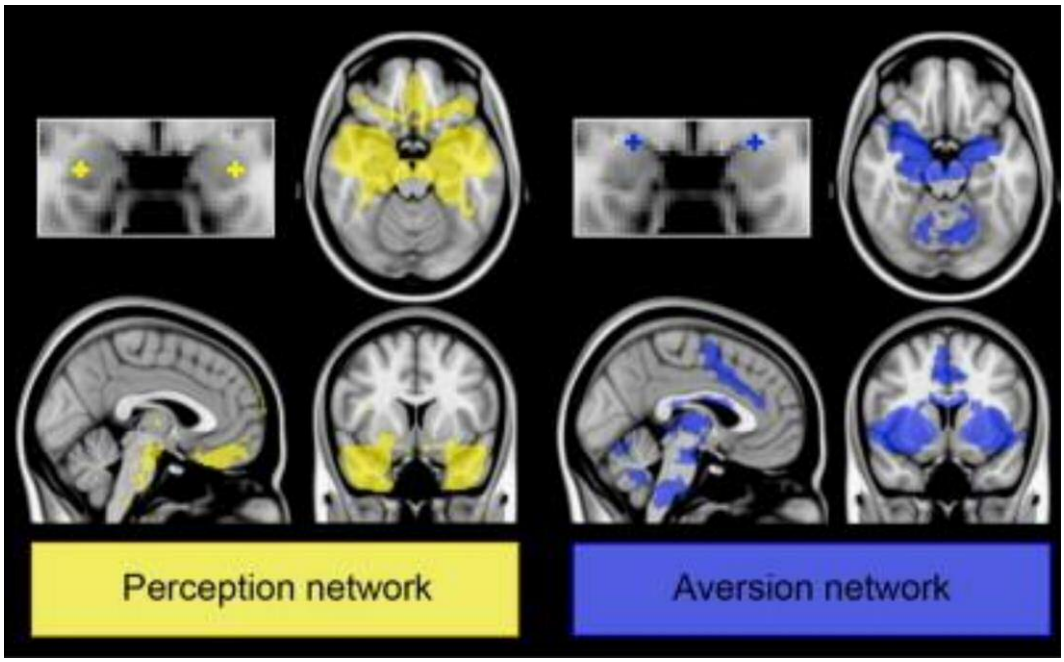

Figure 1.3. The Perception and Aversion networks. Large-scale social cognitive networks showing functional connectivity with sub-portions of the amygdala. Crosses show seed amygdala regions used for connectivity analyses. *Adapted from Bickart, et al., 2014*

Motor empathy may be a fundamental component of empathic functioning, yet, while some argue that motor empathy may be necessary but not sufficient to account for empathic behaviour (Decety & Jackson, 2004), others propose that it may not even be necessary (de Vignemont & Singer, 2006). Motor empathy may have an important role in empathy as the primary mechanism through which observers actually share in the emotion of their target, a key aspect of many definitions of empathy (de Vignemont & Singer, 2006; Hillis, 2013; Walter, 2012; Zaki & Ochsner, 2012). Indeed the motor-based empathy model, the Perception Action Model, provides a compelling account for basic emotion congruence however it fails to account for evidence showing that factors such as motivation or self-relevance can impact on or even prevent supposed automatic neural mirroring (Fox et al., 2013; Singer et al., 2006). Motor empathy is thus limited as an explanation of empathy as emotion contagion and mimicry may not facilitate an *understanding* of others. Though experiences may be common they may instead draw one's focus to one's own experience rather than to that of the other, akin to Davis' (1983) notion of 'personal distress'. If we are swimming in the sea and those around us become profoundly afraid we are likely ourselves to become afraid via emotion contagion. Yet, it is unlikely that this fear and consequent concern is

for those around us, we are now afraid for ourselves; even if we are entirely unaware of *why* those around us are afraid.

The awareness that an emotion is not principally the experience of the self, but belongs to another is argued to be a vital component of human empathy (de Vignemont & Singer, 2006; Decety & Jackson, 2004). This ability to separate ourselves and others and attribute experiences to another is critical for empathy, but may not be present in cases of emotion contagion and mimicry. As such, in some models contagion and mimicry have been argued to be separate from empathy (de Vignemont & Singer, 2006; Decety & Jackson, 2004) and the like-for-like emotion sharing that occurs in mirroring or contagion has been argued by others to not be a necessary condition of empathy (Zahavi & Rochat, 2015), in line with the philosophical position of Edith Stein (Stein, 1989). As a result of these considerations, motor empathy will not be focused upon in this thesis.

Mirroring (in the sense of state matching) will not be considered in depth in this thesis as there are questions over its role in empathy and because methodologically it is challenging to test. From a methodological point of view, we are incapable of truly knowing what another is experiencing, to know that an observer is experiencing emotions in line with those of a target requires a detailed knowledge of the emotional experience of the observer, something hard if not impossible to obtain. Imaging may not overcome this issue as the conclusion that matching activity patterns indicates matching experience is intrinsically flawed. Individuals who are congenitally insensitive to pain and thus have no personal experience of pain have been seen to show activation within the 'pain network' while they view others in pain (Danziger, Faillenot, & Peyron, 2009): an observation that is not explainable as a sharing of experience on the basis of their own past experience. Further to this, inferring common experience from overlapping of sites of neuronal activity walks dangerously close to relying on "bad reverse inference" (Lieberman & Eisenberger, 2015). This is the inference that if I feel X and site A is active then I am experiencing the same thing if A is active when I observe Y. This is a potentially major issue in the interpretation of neuroimaging data (Poldrack, 2011). Consistent with the need for caution in interpreting such state matching accounts, spatially overlapping activity that is seen when experiencing and observing pain has been seen to be distinguishable using multivariate pattern classification and functional connectivity methods. Thus while such activity may be spatially overlapping, it is nevertheless distinguishable (Woo et al., 2014; Zaki, Ochsner, Hanelin, Wager, & Mackey, 2007).

For the reasons outlined this thesis will not focus on the matching or mirroring of the internal experiences of others, and be intentionally noncommittal with regard the experiential component of empathy. The sharing and matching of emotional state (emotional 'resonance') will not be viewed as a necessary component for the behaviours or processes of consideration. This thesis will instead be concerned with the explicit *understanding* of the experiences of others. As such, the posited sharp distinction between sympathy and empathy (Singer & Lamm, 2009) will not be drawn within this thesis. There is a clear conceptual distinction between the two, empathy involves feelings that are isomorphic to those of the observed, while sympathy involves different feelings, such as sadness for someone in pain (Decety, 2011; Paulus, Müller-Pinzler, Westermann, & Krach, 2013; Singer & Lamm, 2009). The distinction will not be drawn here as the difference between the two is difficult to determine without knowing the exact nature of the observer's experience.

1.2.3.1.2 Emotion recognition or perceptual empathy

As emotion expressions are a principle source of information about the emotional state of another (Ekman, 1992a) there is little question that the ability to interpret others' expressions of emotion plays a key role in the ability to empathise. Yet while in some models of empathy emotion recognition is tightly intertwined with motor empathy, emotion recognition has been posited to be separable from the motor component of empathy (Blair, 2005). In accounts of motor empathy and in simulation theory, emotion recognition is tied up with motor empathy as the observation of an emotional state is proposed to automatically activate that state in the self (Preston & de Waal, 2002; Heberlein & Atkinson, 2009), leading to a direct form of understanding. Some evidence supports this proposal as emotional facial expressions appear automatically mimicked even when sub-consciously viewed (Dimberg, Thunberg, & Elmehed, 2000). Yet, alternative models of empathy, such as that proposed by Blair (2005) forward that emotion recognition is distinct from emotion contagion as it emphasises the comprehension or interpretation of the state of the other, not the experience of the emotion of the other such models focus heavily on emotion recognition and the decoding of facial emotion expression in particular (see Figure 1.3 for neural regions involved in the "Perception network") (Blair 2005). The proposed separation of motor mirroring and emotion recognition means that while emotion recognition may rely, in some instances, on emotion contagion, emotion contagion does not equate to emotion recognition. For example, human babies may cry when they hear others cry, but they may not understand that the other is experiencing distress and as such would not be described as showing emotion recognition.

Evidence for such a distinction is found in the presence of intact emotion recognition in individuals who are themselves unable to produce emotion responses, such as those with facial paralysis (Bogart & Matsumoto, 2010). Indicating that while there may be some interplay between the two processes, emotion recognition is not dependent on motor mirroring.

Emotion recognition is dependent upon the perception of emotional signals given out by another such as in their vocal tone, facial expression or posture. For this reasons, emotion recognition can be thought of as perceptual empathy, as it allows for the understanding of the emotional state of another but the input is entirely from a perceptual source. This is as opposed to cognitive empathy, as described below, where information can be obtained without perception of the other individual. Perceptual empathy is distinct from emotion contagion as it involves an explicit understanding of the emotional state of the other. Unlike in the case of mirroring, perceptual empathy requires an understanding of the state of another but not a matching experience *per se.* As such, because of the challenges of investigating individual's internal states, and the issues with mirroring accounts more generally, this thesis will primarily focus on the perceptual empathy (emotion recognition or decoding) aspect of affective empathy. In line with the cognitive neuroscience approach discussed previously, perceptual empathy and emotion recognition are not in themselves sufficient to encapsulate empathy more broadly but understanding perceptual empathy will inform our understanding of empathy more widely by providing insight into how a principle source of information regarding the emotions of others is processed.

1.2.3.2 Cognitive empathy

Most models of the cognitive components of empathic functioning broadly agree on the presence of a cognitive component of empathy (Blair, 2005; Chakrabarti & Baron-Cohen, 2006; de Waal & Preston, 2017; Shamay-Tsoory, 2011; Shamay-Tsoory et al., 2009; Zaki & Ochsner, 2012). This cognitive component of empathy enables individuals to understand and predict the internal state of others, even when the other is not physically present and as such there are no perceptual cues to their mental state. This ability is critical for understanding the emotions of others in situations such as when reading a story or listening to an individual relaying the experiences of others. Cognitive empathy is additionally critical for the interpretation of another's state based on contextual information and prior knowledge, such as understanding that an individual attending a funeral is likely to be experiencing grief.

Cognitive empathy is commonly described as being synonymous with mentalising (Blair, 2005; Shamay-Tsoory, 2011; Shamay-Tsoory et al., 2009; Zaki & Ochsner, 2012). Mentalising, often termed theory of mind, is the conception of mental experiences or states, such as thoughts, feelings and beliefs, and the attribution of these to ourselves and others (Premack & Woodruff, 1978). As touched upon previously, cognitive empathy or mentalising may occur in the absence of perceptual input regarding another individual, this means that it is possible to formulate an understanding of how another is feeling without needing to see or hear them. Mentalising makes this possible by enabling individuals to formulate a prediction or theory regarding the experience of another based on information such as their behaviour, the context in which they are, personal preferences and personality. Mentalising is critical for, or synonymous with, cognitive empathy as we are only able to understand the experiences of others and the causes of these experiences if we understand that others have mental experiences different from our own and can formulate representations of what these may be.

Previously, mentalising, or theory of mind, have been conceptualised in several ways, yet within the literature there are two principle standpoints regarding the mechanisms of mentalising, these are termed 'theory-theory' and 'simulation-theory'. 'Theory-theory', posits that individuals form hypotheses about the experiences of others from available information, while 'simulation-theory' proposes that the experiences of others are understood by drawing on memory and understanding of what we ourselves would do in a given situation (sometimes referred to as 'experience projection')(Apperly, 2008; Gallese, 2007; Gallese & Goldman, 1998; Leslie, Friedman, & German, 2004; Schaafsma, Pfaff, Spunt, & Adolphs, 2015). A comprehensive review of the mentalising literature will not be given here as it is vast. Nor is a specific position intentionally taken with regards to the theory-theory/simulation-theory debate. It is however noteworthy that the mentalising literature has historically focused on development rather than mature functioning (Apperly, 2013; Baron-Cohen, Leslie, & Frith, 1986; Leslie et al., 2004) and that some have argued that it is experience projection not mental state inference that is closely related to empathy (Schaafsma et al., 2015). This argument is partly based on postulation made by some simulation-theorists that the mirror neuron system has a key role in mentalising (Gallese & Goldman, 1998).

A range of experimental methods are used for the assessment of mentalising. These assessments range from determining simply the ability of an individual to understand that others can hold different beliefs and perspectives to the self, through to assessments that tap the level of understanding of the mental state of another (for an in-depth review see Achim et al., 2013,

Schurz et al., 2014). A classic category of mentalising task is the false belief task, these tasks are typically used with children and assess the ability to understand that another may hold in inaccurate belief. Classic false belief tasks involves a character placing an item in one location and then not observing the item being moved by another individual (Wimmer & Perner, 1983). The task involves the observer predicting where the character that originally placed the item will expect it to be. The task is argued to be sensitive to mentalising as it requires the observer to be able to understand that the characters can have false beliefs regarding where an item is. The ability to appreciate that others can hold beliefs different from ourselves and that they may hold false beliefs may be a critical component of mentalising yet on its own does not constitute cognitive empathy. Mentalising tasks that better capture cognitive empathy are those that instead require the attribution of mental and emotional states to others. These tasks often involve the selection of images that complete a story told through a series of cartoons (Vollm et al 2006)

While in empathy models mentalising may fit within the scope of cognitive empathy, models of mentalising have been proposed that sub-divide mentalising (Abu-Akel & Shamay-Tsoory, 2011; Brothers & Ring, 1992; Tager-Flusberg & Sullivan, 2000). This will not be explored in great detail here, save to say that some posited components of mentalising fit within my description of affective rather than cognitive empathy, according to the model of empathy outlined here. For example, in one model mentalising is argued to be divisible into perceptual and cognitive components (Sabbagh, 2004; Tager-Flusberg & Sullivan, 2000). For the purposes of this thesis, these two components are *not* both thought to be components of cognitive empathy. Instead mental state decoding, being based on perceptual input, is considered to be far more in line with perceptual empathy, in line with previous proposals (Sabbagh, 2004; Tager-Flusberg & Sullivan, 2000). As such, some existing studies of mentalising utilise tasks that would here be considered to be more in line with affective than cognitive empathy, such as those that involve mental state decoding based on facial expression (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Sabbagh, 2004; Tager-Flusberg & Sullivan, 2000).

1.2.3.3 Top-down or bottom-up?

Instead of being seen as entirely different processes, the posited components of empathic functioning may best be viewed as levels within a processing stream. Clearly, component processes of complex functions such as empathy or mentalising will work in concert with each other in every day behaviour. In a levels-based account, perceptual empathy can be seen as

bottom-up processing with perceptual input leading to decoding of the emotional expressions of others. Cognitive empathy may however be top-down, as complex cognitive abilities such as introspection may facilitate thoughts about the causes and consequences of the emotional states of others, and affective responses in the self (de Waal & Preston, 2017). Cognitive and perceptual components of empathy may thus broadly be considered to be different sources of input into a two-way empathic processing system.

The proposition that cognitive empathy is a higher level of processing is partly based on the idea that cognitive empathic processes may be layered on top of the developmentally and phylogenetically older perceptual or affective empathy system (Chakrabarti & Baron-Cohen, 2006; de Waal & Preston, 2017). According to this idea, early affective systems may provide scaffolding upon which individuals can develop their cognitive understanding of others (Chakrabarti & Baron-Cohen, 2006). Top-down processes may include further complex cognitive processes such as executive function and cognitive control which may be necessary for inhibiting the observer's own perspective and making self-other distinctions (de Vignemont & Singer, 2006; Decety & Lamm, 2006). These cognitive components regulate, control and provide contextual information for empathy and are proposed to be intertwined in the generation and modulation of empathy (Decety & Lamm, 2006). Such a broader system of processes may be required for some aspects of empathic functioning but will not be directly considered here as their central function is not facilitating an understanding of the experiences of others.

1.2.3.4 Neural regions involved in empathic functioning

Functional specialisation within the brain, where-by specific brain regions are involved in specific cognitive functions, is well established (Felleman & Van Essen, 1991; Squire, 1992). Consistent with this, empathy research has tended to focus on functional segregation primarily using functional imaging methods to identify regions of cortex that appear involved in empathy due to showing increases in levels of activity during a specific empathy tasks (Lamm et al., 2011).

1.2.3.4.1 The affective empathy system

As touched upon earlier, the affective empathy system has been associated with a *network* of neural regions, predominantly located in the frontal and temporal lobes. In the original PAM (Preston & de Waal, 2002), this empathy system was proposed to be supported by a network of 'mirror' areas and regions involved in the limbic circuit, spread across the frontal and temporal

lobes. Others have however argued that, while mirror neurons may provide a physiological mechanisms for emotional resonance, there is no clear evidence for their accounting for empathy (Decety, 2010). Instead, consistent with the remaining non 'mirror' regions proposed in the PAM (Preston & de Waal, 2002), empathy may require reciprocal connectivity between a complicated and distributed network of regions including the amygdala, insular and prefrontal cortex (Decety, 2010), areas identified as part of the social brain in early social neuroscience work by Brothers (1990).

See Figure 1.3 for neural regions associated with emotion recognition (The Perception network) and chapter 2 for further discussion of neural regions involved in affective components of empathy.

1.2.3.4.2 The cognitive empathy system

The cognitive empathy system, here synonymous with the mentalising system, is underpinned by a network of regions primarily found along the cortical midline (including medial prefrontal cortices, PCC and Precuneus) and TPJ (Dodell-Feder, Koster-Hale, Bedny, & Saxe, 2011; Gallagher et al., 2000; Koster-Hale & Saxe, 2013; Saxe & Kanwisher, 2003; Schurz et al., 2014) (See Figure 1.4). Though variability is seen across tasks defined as assessing mentalising (Achim, Guitton, Jackson, Boutin, & Monetta, 2013), these regions reliably show increases in activity during tasks requiring inferences to be made about the reasons for another's feelings or actions (Schurz et al., 2014; Spunt & Adolphs, 2014; Spunt & Lieberman, 2012) or reflection on the experiences of others

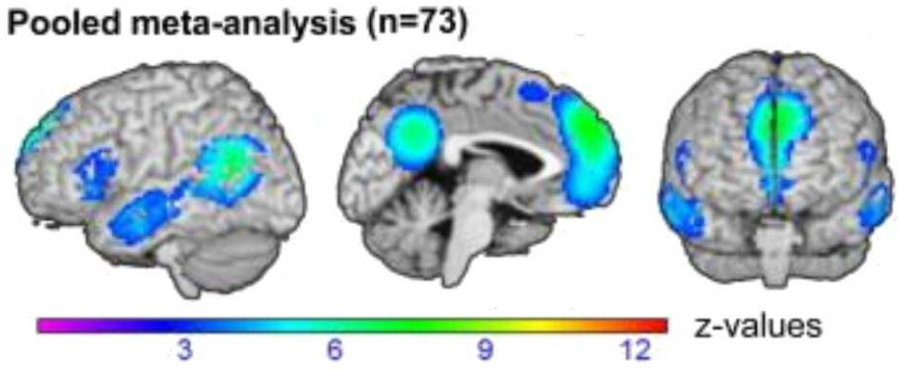

Figure 1.4 Regions of functional activity in a pooled meta-analysis of mentalising tasks. *Adapted from Schurz et al 2014*

(Lamm et al., 2011).

Consistent with arguments for a dissociation between mental and emotional components of mental state reasoning (Abu-Akel & Shamay-Tsoory, 2011; Brothers & Ring, 1992) specific regions within this network may be particularly critical for the understanding of emotional as opposed to mental states. Regions located more ventrally in the medial frontal cortex appear more involved in emotion inference while more dorsal and lateral regions appear more involved in belief and intention inference (Poletti, Enrici, & Adenzato, 2012; Shamay-Tsoory & Aharon-Peretz, 2007). Further work is however needed to clarify the presence of such dissociations.

For further discussion of neural regions involved in cognitive components of empathy see chapter 3.

1.2.4 The neurocognitive networks underlying Empathy

As highlighted, distributed networks of regions, rather than single functionally specialised areas, may be responsible for complex cognitive functions such as empathy (Behrmann & Plaut, 2013). Indeed such complex functions may occur at the level of large-scale neural networks (Mesulam, 1990; Tononi, Edelman, & Sporns, 1998). For this reason the brain may best be thought of as a 'connectome' (Sporns, Tononi, & Kotter, 2005), with the intercommunication of regions as well as their individual functioning being critical for the facilitation of cognitive functioning. This means that considering the network structure underpinning a complex functions such as empathy is critical to social cognitive neuroscience (Sporns et al., 2005).

Within a network, functioning is reliant on the ability of the network's constituent elements to communicate and functionally integrate. As such the ability of these regions to functionally interact would be expected to impact on the resulting superordinate process. Consistent with this proposal, superordinate processes may be dysfunctional if the interconnections between their functional elements become broken or function suboptimally, even if the elements themselves are functional. Such has been described to be the case in a number of clinical groups suh as congenital prosopagnosia (Behrmann & Plaut, 2013) and 'disconnection syndromes' more generally (Catani & Mesulam, 2008).

The distribution of functional regions associated with cognitive and perceptual components of empathic functioning suggests that anatomically distributed but integrated functional networks may underpin both. Indeed there is general agreement that empathic processing depends on an array of brain structures and systems (Decety, 2011) and as such, may be described as a network function (Bernhardt & Singer, 2012; Hillis, 2013; Shamay-Tsoory, 2011). The consideration of the network structure of empathy has however been relatively limited. In particular, sparse consideration has been given to the role that connections between functional regions may have on empathic functioning. Work which has considered network-level functioning in empathy has supported the importance of network-level functional connectivity, indexed by signal covariance on resting state functional magnetic resonance imaging (fMRI), between cortical regions associated with empathy in broad self-report assessments of empathising (Cox et al., 2012; Takeuchi et al., 2014). Yet, despite this work there remains relatively little work that has looked at the role of brain structural connectivity in mediating empathic functioning.

1.2.4.1 White matter and empathy

Within the brain, white matter forms the connections that bind spatially distant functional regions. Consistent with a key role for connectivity in facilitating functioning, it has been established that white matter structure has a critical role in mediating functional connectivity and communication between brain regions (Boorman, O'Shea, Sebastian, Rushworth, & Johansen-Berg, 2007; Greicius, Supekar, Menon, & Dougherty, 2009; van den Heuvel, Mandl, Luigjes, & Hulshoff Pol, 2008).

Relatively little attention has been paid to the role of white matter in cognition, however evidence suggests that white matter has a key role in many cognitive functions. In humans, white matter shows a protracted development, not fully maturing until the third or even fourth decade of life (Lebel & Beaulieu, 2011; Lebel et al., 2012). The development of white matter across this period appears to have an important impact on the development of many cognitive abilities including language (Lebel & Beaulieu, 2009; Tamnes et al., 2010), memory (Mabbott, Rovet, Noseworthy, Smith, & Rockel, 2009) and response inhibition (Madsen et al., 2010; Treit, Chen, Rasmussen, & Beaulieu, 2014). Beyond development, white matter may further continue to influence functioning. White matter microstructure appears to change in response to experience (Scholz, Klein, Behrens, & Johansen-Berg, 2009; Tang et al., 2010), partly as a result of neural activity dependent processes (Fields, 2008), and relates to individual differences across a number of cognitive functions (Hodgetts et al., 2015; Metzler-Baddeley et al., 2012; Postans et al., 2014).

Emerging evidence further suggests that white matter microstructure may be related to psychiatric symptoms such as anxiety (Kim et al., 2011; Kim & Whalen, 2009) and may indeed be related to the presence of psychiatric conditions (Fields, 2008; Whalley et al., 2015). White matter pathology also has a major role in the development of neurological conditions such as multiple sclerosis (Frischer et al., 2015; Kutzelnigg et al., 2005), and disturbs cognitive functioning in a range of clinical groups (Filley & Fields, 2016). White matter therefore appears to have an important role in supporting a cognitive functioning.

To date, few studies have considered the role of white matter structure in empathy. Those that have, reveal there to be associations between empathic functioning and microstructural properties of cerebral white matter, using self-reported assessments of empathy (Fujino et al., 2014; Parkinson & Wheatley, 2014). Lesion work has further shown that disruption to white matter can substantially impair empathic functioning (Herbet et al., 2015; Oishi et al., 2015). In particular, two lesion studies have shown evidence, both for a key role for white matter in empathic functioning and a potential dissociation of the white matter tracts that may support cognitive and perceptual components of empathy. In individuals with relatively selective white matter damage, resulting from glioma or stroke, damage to the right uncinate fasciculus (UF) has been shown to be related to affective empathy impairments (Herbet et al., 2015; Oishi et al., 2015), while left sided cingulum bundle (CB) lesions have been linked to impairments in cognitive empathy (Herbet et al., 2015). While there is limited work in this area, these studies suggest that the structure of white matter may indeed play a role in empathic functioning (See further discussion of these findings in chapters 2 and 3).

1.3 Structural imaging of white matter

Brain imaging provides an exciting avenue through which to (indirectly) study network connectivity. In this thesis I will focus on structural connectivity, though both structural and functional connectivity can be investigated. Structural connectivity is the physical connectivity between distant brain regions, which is principally supported by neural white matter tracts. While invasive methods can directly trace white matter connections (Hau et al., 2016), diffusion weighted imaging (DWI) is the principle method by which white matter fibres are investigated in the human brain *in-vivo*. It therefore will be the method utilised in this work.

1.3.1 Diffusion-weighted magnetic resonance imaging

1.3.1.1 Overview

DWI is a nuclear magnetic resonance (NMR) technique that can be used to obtain information about the brain based upon the motion of water molecules within brain tissue. DWI is possible because water molecules are in a state of constant motion and as such change location over time (See Figure 1.5). In DWI, the NMR signal is sensitive to changes in the location of water molecules, such that greater movement results in lower NMR signal (Mori & Zhang, 2006). Because the change in NMR signal is related to the distance that water molecules move, quantifying the loss of signal can be used to image the relative ability of water to move in given orientations within a structure (Jones, 2008). This can be used to assess brain structure because, within biological tissue, there are many structures that impede diffusion, including, importantly, the membranes of neuronal axons. Water is not able to freely diffuse across neuronal membranes and so water diffusion is restricted principally to orientations perpendicular to cell membranes (See Figure 1.5A).

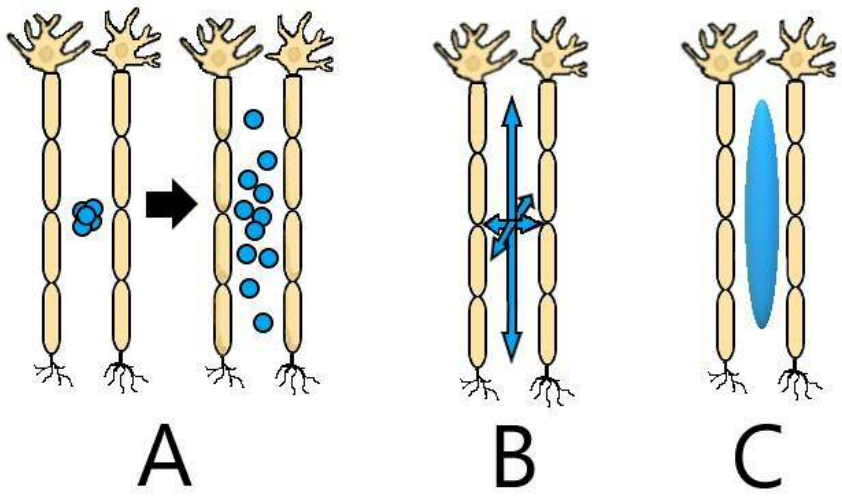

Figure 1.5 Pictorial representation of diffusion imaging concepts. (A) Diffusion between neurons; (B) Principle diffusion direction and orthogonal diffusion in X, Y and Z orientations; (C) Diffusion tensor.

For the purposes of neuroscience research, water diffusion as measured using DWI tends to be characterised using the diffusion tensor model, referred to as diffusion tensor imaging (DTI). For the purposes of DWI, DTI, and brain imaging in general, the brain is sub-divided into cubes known as voxels. DTI involves collecting measures of diffusion in multiple orientations for each voxel within the brain (Mori & Zhang, 2006). Multiple orientations are necessary as DWI can only capture diffusion along a single orientation yet within real-world structures water is able to diffuse across three dimensions. As such, to obtain a three dimensional representation of diffusion, diffusion weighted images need to be obtained in at least three orthogonal orientations, akin to X, Y and Z axes within a graph (See Figure 1.5B). In DTI values for diffusion across these orientations are used to calculate a mathematical entity called a tensor. Diffusion tensors can be mathematically described by three values known as eigenvalues. In DWI these eigenvalues are related to the extent of diffusion along three orthogonal orientations, the principle diffusion direction, the orientation of maximal diffusion, and the two orientations that sit orthogonal to it (Jones, 2008; Stieltjes et al., 2001). Thus, a diffusion tensor is a description of diffusion within three-dimensional space (Jones, 2008), which can be graphically represented as an ellipsoid (See Figure 1.5C). In this conceptualisation, a tensor in a voxel where diffusion is equally possible in all directions, called isotropic diffusion, has the shape of a perfect sphere (See Figure 1.6). Where diffusion is not equal in all directions, termed anisotropy, the tensor takes the shape of an ellipsoid where the longest dimension corresponds to the orientation of the greatest diffusion (Figure 1.6). In anisotropic diffusion the relative width of the tensor ellipsoid is related to the diffusion perpendicular to the principle diffusion direction (see Figure 1.5B&C).

1.3.1.2 Diffusion metrics

From DWI a number of metrics can be calculated, these describe diffusion within a given voxel and are related to the microstructural properties of underlying white matter fibres (Jones, 2008; Mori & Zhang, 2006). The most commonly utilised metric taken from DTI is fractional anisotropy (FA). FA is a metric of the extent to which diffusion within a given space diverges from isotropic diffusion (Mori & Zhang, 2006). Values for FA range between zero, being perfect isotropic diffusion, and one, being diffusion occurring solely along the principal diffusion direction (See Figure 1.6). Unfortunately it is not known what the exact relationship is between metrics such as FA and variability in biological structures, such as white matter myelination (Jones, Knösche, & Turner, 2013) (see chapters 2 and 3 for further discussion), though it has been highlighted that it is

not uncommon for FA to be inaccurately described as being related to the 'integrity' of white matter (Jones, Christiansen, Chapman, & Aggleton, 2013). Despite this lack of understanding of the relationship between diffusion imaging metrics and the biological structure of white matter, diffusion imaging can give us valuable information about the brain (Fields, 2008; Seehaus et al., 2015). Diffusion imaging methods can be used to investigate differences between groups in terms of their white matter (Craig et al., 2009; Le Bouc et al., 2012; Lu, Lee, et al., 2013) and to investigate relationships between white matter microstructure and cognitive functioning (Assaf & Johansen-Berg, 2017; Hodgetts et al., 2015; Postans et al., 2014; Roberts, Anderson, & Husain, 2013).

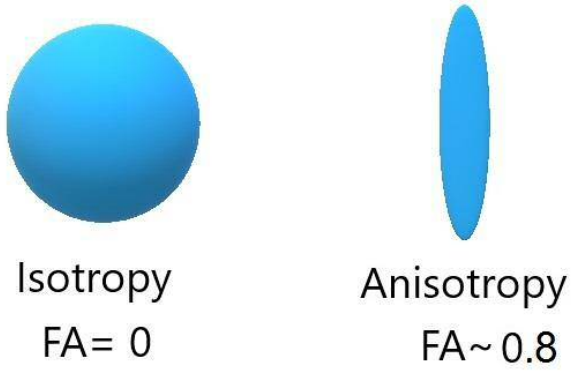

Figure 1.6. Visual representation of diffusion tensors representing Anisotropy and Isotropy

1.3.1.3 Tractography

DWI can be used to virtually reconstruct white matter pathways within the brain thanks to the relationship between the orientation of diffusion and the orientation of white matter fibres. Because diffusion is greatest perpendicular to cell membranes, DWI is particularly valuable for the investigation of structures in which cells or fibres run in parallel, such as neural white matter (Jones, Horsfield, & Simmons, 1999). In such structures the orientation of the principle diffusion direction will be the same as the orientation of the fibres (Basser, 1995; Basser, Mattiello, & LeBihan, 1994). By tracking across the brain following principal diffusion directions we can thus track the path of white matter tracts. This enables the virtual reconstruction of white matter bundles, called tractography, and the isolation and investigation of specific white matter pathways within the brain (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Catani, Howard, Pajevic, &

Jones, 2002; Conturo et al., 1999). White matter tracts extracted in this way show a high degree of fidelity to white matter structures as identified in post-mortem work (Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012; Thiebaut de Schotten et al., 2011).

Tractography can be carried out using one of two methods, deterministic or probabilistic. In deterministic tractography, tractography is carried out by taking the principle diffusion direction for each voxel and following these through the brain, tracking a single path to see if there is a pathway by which two points can be reached (Jones, 2010). To do this, a seed region, from which to initiate tracking, is necessary as is at least one additional regions of interest (ROI), through which the pathway of interest must pass. In deterministic tractography, constraints may be placed upon the tracking, such that anatomically implausible tracts are not reconstructed, such as ones that enter grey matter (Jones, 2008). Probabilistic tractography is similar to deterministic but instead of constructing single pathways between points based on principle diffusion directions, connections and steps in probabilistic tractography are estimated based on a distribution of possible fibre orientations, based upon the orientation of the principle diffusion direction (Jones, 2010). For this reason, in probabilistic tractography multiple pathways are calculated, each of which has a different level of probability. Probabilistic tractography is summarised voxel by voxel as the percentage of possible pathways between the points that pass through each voxel.

As tractography based on the tensor model is not a perfect representation of the underlying cellular structure of the brain, there are a number of issues with methods of fibre reconstruction using the diffusion tensor approach. Firstly, at the resolution of DWI, voxels may contain fibres with several different orientations. Yet, by considering only the principle diffusion direction, the classic tensor model fails to account for such crossing fibres. To overcome this issue, high angular resolution diffusion imaging (HARDI) can be carried out, where many diffusion orientations, beyond the three necessary for DTI, are collected for each voxel (Hosey, Williams, & Ansorge, 2005). Diffusion orientations are always collected in multiples of three (the three orthogonal orientations of X, Y and Z), and the more orientations that are collected the more accurate a representation of the diffusion within the voxel. Using the increased level of information provided by such high angular resolution data, it is possible to mathematically reconstruct multiple pathways within a single voxel. Using HARDI data crossing fibres can be used to reconstructed using methods such as constrained spherical deconvolution (CSD), as such HARDI and CSD will be used here (Tournier, Calamante, Gadian, & Connelly, 2004; Tournier et al., 2008).

1.3.1.4 Tract Based Spatial Statistics (TBSS)

The ability to specify and investigate specific white matter pathways and consider metrics relating to their microstructure is a major strength of DWI. For this reason 'native space' tractography can be considered the optimal method for addressing questions relating to specific white matter pathways in individual brains. Yet, when hypotheses are not present with regards to specific anatomical regions, a whole brain, voxel-based method of analysis of DWI can be utilised, such as tract based spatial statistics (TBSS) (Smith et al., 2006). Using TBSS, diffusion infomraiton is warped onto a standardised white matter skeleton and microstructural metrics of white matter are considered across the whole brain by running correlations within this core white matter skeleton. In addition to issues of specificity due to the warping involved in TBSS, TBSS analyses are victims of the multiple comparisons problem, as comparisons are run across a large number of voxels. This increases the risk of producing false positive results but also, due to the need to control for the large number of comparisons, makes it less sensitive to true relationships, especially if these effects are small. Further to this, using TBSS it is hard, if not impossible, to conclusively determine the specific white matter in which structures effects lie due to issues of warping and the presence of overlap between white matter tracts.

1.3.1.5 DWI in this thesis

The first two chapters of this thesis will address the relationship between white matter microstructural metrics and individual differences in performance on tasks sensitive to cognitive components of cognitive and affective empathy. Because of the presence of specific tract-related hypotheses, diffusion based tractography will be utilised to consider specific tracts of interest. TO maximise the accuracy of these tracts in regions with crossing fibres, HARDI and CSD-based tractography will be utilised.

1.4 Neurodegeneration: The perturbation of neurocognitive networks

1.4.1 Neurodegeneration as a clinical model for the study of social cognition

Across the history of cognitive neuroscience, from the study of Phineas Gage to HM (Damasio et al., 1994; Scoville & Milner, 1957), individual case studies and the study of the impact of lesions on functioning have had a critical role in advancing our understanding of functional specialisation (Rosenbaum, Gilboa, & Moscovitch, 2014). Within neurology and neuropsychology, studying the consequences of pathology is a well-established method of investigating structure to function relationships. Dissociations that emerge from such work are valuable for the identification of the cognitive components of complex cognitive functions (Shallice, 1988). It is feasible that, in a similar way, studying clinical groups who show network-based neural alteration may aid our understanding of neurocognitive networks and their role in cognitive functioning. One avenue for investigating the role of brain networks in cognitive functioning is through the investigation of neurodegenerative disease.

1.4.1.1 Network selective degeneration in Dementia

'Dementia' is the progressive loss of cognitive functioning due to neurodegenerative disease. The dementias are a major class of neurodegenerative disease, diseases that cause the progressive degeneration of neurons. Dementias are a major health concern across the globe as dementia is highly age related and thus, with an aging population, dementia is an increasingly prominent cause of death and morbidity. In many forms of dementia, disease is related to the accumulation of miss-folded protein within the brain, ß-amyloid and tau in Alzheimer's disease (AD) (Glenner, 1989) and ubiquitin, TDP-43 or tau in Frontotemporal lobar degeneration (FTLD) (Mackenzie et al., 2010; Shi et al., 2005). The most prominent theory of dementia is that these protein accumulations are toxic and lead to neural death and dysfunction, which leads to cognitive dysfunction (Carter & Lippa, 2001; Hardy & Higgins, 1992).

The study of dementia may have particular value in developing our understanding of network functions, as neurodegenerative diseases, including the dementias, appear to show degeneration in cohesive, functionally integrated, large-scale neural networks (they are 'network pathologies'). In many forms of dementia, there appear fairly consistent patterns of degeneration with pathological processes appearing to initially impact focal sites (Braak & Braak, 1991; Braak et al., 2006; Seeley et al., 2008) and specific neuronal populations (Seeley et al., 2006). Yet, from these sites degeneration appears to progress along brain networks with a predictable pattern of degeneration observed using both histology (Braak & Braak, 1991; Braak et al., 2006) and neuroimaging (Greicius & Kimmel, 2012; Seeley, Crawford, Zhou, Miller, & Greicius, 2009). Rather than degeneration appearing to spread simply based on proximity, these sets of regions appear to sit within structurally connected, functionally integrated networks (Seeley et al., 2009); (Goedert, Clavaguera, & Tolnay, 2010; Hardy & Higgins, 1992; Jucker & Walker, 2013; Saper, Wainer, & German, 1987). Dubbed the network degeneration hypothesis, this observation is the basis of a theory, which proposes that neurodegeneration and neurodegenerative pathology may selectively track networks of brain regions that functionally interact.

Neuro-imaging has provided support for the network degeneration hypothesis (Raj, Kuceyeski, & Weiner, 2012; Zhou, Gennatas, Kramer, Miller, & Seeley, 2012), showing that patterns of neurodegeneration and protein deposition across a number of dementias exhibit marked overlap with sets of brain regions that showed functional connectivity in healthy adults at rest (Buckner et al., 2005; Seeley et al., 2009). Such observations have led to the proposal that it may be this distribution of pathology across networks that dictates disease symptomology and thus clinical category, rather than the specific form of molecular pathology (Lanata & Miller, 2016).

The network selectivity seen in neurodegenerative diseases has led to the proposal that neurodegenerative diseases and FTD in particular may be an ideal clinical model through which to study neural circuits underlying empathic cognition (Elamin, Pender, Hardiman, & Abrahams, 2012; Ibanez, Kuljis, Matallana, & Manes, 2014; Levenson, Sturm, & Haase, 2014; Zhou et al., 2012). Because neurodegenerative disease may selectively impact functionally specific neural networks, studying the symptoms of neurodegenerative disease may provide us with insight into the functional role of these networks and the behavioural consequences of damage to them. Of the neurodegenerative diseases, FTD is particularly relevant for the investigation of social and empathic functioning as it appears to selectively affect networks implicated in social behaviour and empathy (Agosta, Scola, et al., 2012; Boccardi et al., 2005; Cerami et al., 2014; Seeley et al.,

2008; Seeley et al., 2009). Indeed FTD has been highlighted repeatedly as having potential value as a model for studying the relationship between brain networks and social cognitive functioning (Elamin et al., 2012; Ibanez et al., 2014; Levenson et al., 2014; Seelaar, Rohrer, Pijnenburg, Fox, & van Swieten, 2011; Seeley, Zhou, & Kim, 2012; Zhou et al., 2012).

1.4.2 Frontotemporal Dementia

1.4.2.1 Background to FTD

Frontotemporal dementia is an umbrella term for a group of dementias that affect the frontal and temporal lobes. Depending on the variant of FTD with which an individual suffers, initial symptoms may be word finding problems, problems with producing fluent language, or changes in personality and social behaviour ("Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups," 1994; Neary et al., 1998). The network structure of the brain may have a particularly important role in FTD, as FTD can be caused by the accumulation of a number of different proteins (Mackenzie et al., 2010; Shi et al., 2005) and as such there is no one-to-one relationship between the type of protein that accumulates and the resulting symptoms (Seelaar et al., 2011; Shi et al., 2005). Instead, in FTD the distribution of pathology across networks may dictate symptomology and clinical diagnosis (Lanata & Miller, 2016).

1.4.2.2 Prevalence

FTD is the second most common cause of early onset dementia after AD. Early onset dementia is classified as a dementia with an onset before 65 years of age. There are estimated to be around 42,000 people in the UK living with early onset dementia, accounting for around 5% of all dementia cases (Prince et al., 2014). Reports put the mean age of onset of FTD at around 52-57 years (Johnson et al., 2005; Ratnavalli, Brayne, Dawson, & Hodges, 2002), though disease onset may occur at any point over the age of around 30 (Johnson et al., 2005). In individuals between the ages of 45-64 FTD has a reported prevalence of around 15 per 100,000 (Ratnavalli et al., 2002). FTD is, however, not solely an early onset disease. Some studies have put the prevalence of FTD in older adults to be even higher than that seen in those under 65, with around 3% of those aged over 85 being found to meet diagnostic criteria for FTD (Gislason et al., 2014; Gislason, Sjögren, Larsson, & Skoog, 2003). FTD is estimated to make up around 2% of all dementia cases (Prince et

al., 2014), yet because of potential rates of under diagnosis, particularly in older adults, this may well be an underestimate.

1.4.2.3 Subtypes

FTD encompasses three clinical syndromes, Semantic Dementia (SD), Progressive Non-fluent Aphasia (PNFA) and bvFTD. All of these syndromes are caused by FTLD (Rohrer et al., 2011), a selective pattern of neurodegeneration that primarily impacts on the frontal and temporal lobes. Each FTD syndrome is however associated with a different characteristic pattern of atrophy and symptomology (Agosta, Canu, Sarro, Comi, & Filippi, 2012).

BvFTD is the most common of the variants of FTD, making up between 40-70% of FTD cases (Ioannidis, Konstantinopoulou, Maiovis, & Karacostas, 2012; Rohrer et al., 2011; Seelaar et al., 2008). BvFTD is characterised by changes in personality and interpersonal conduct, with particular impairments in the domains of social behaviour, social interest, empathy and motivation (Neary et al., 1998). Individuals with bvFTD may be socially inappropriate, lacking in emotional warmth and care for others and show marked changes in their personality, tastes and preferences. BvFTD is associated with prominent frontal and ATL degeneration (Pereira et al., 2009; Rohrer, 2012; Seeley et al., 2008)(See figure 1.7).

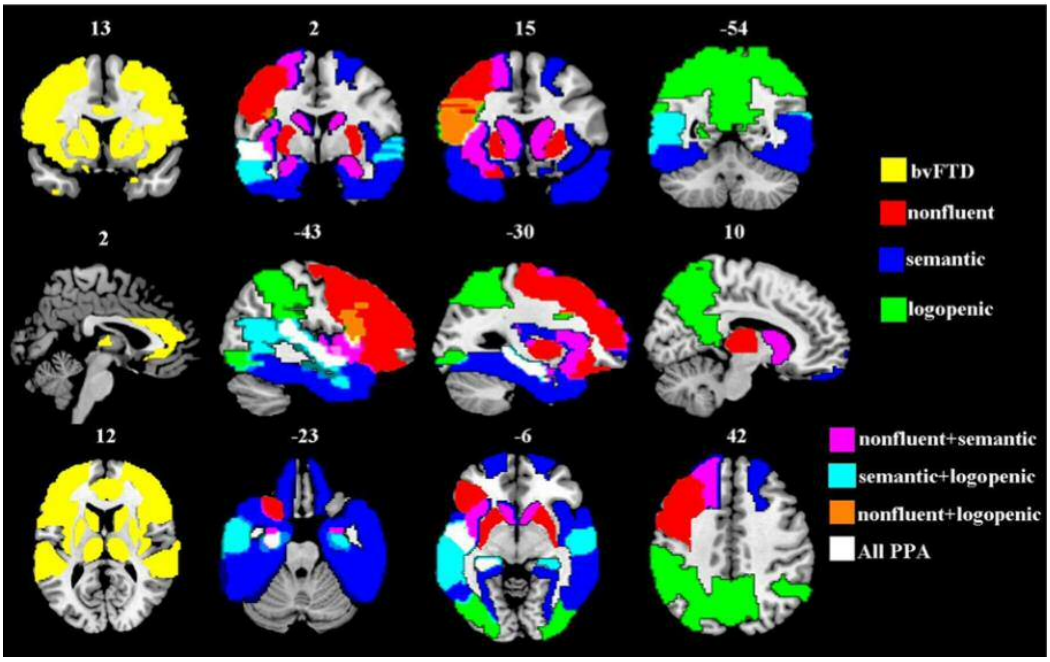

Figure 1.7. Patterns of grey matter atrophy in FTD sub-types as derived from the literature.
bvFTD= behavioural variant of Frontotemporal dementia, PPA = primary progressive aphasia.
Taken from Agosta et al (2012)

SD is the second most common form of FTD and accounts for around 24% of FTLD cases (Rohrer et al., 2011). SD is initially caused by degeneration of the ATL, frequently in the left hemisphere (LH), though as the disease progresses degeneration extends into posterior temporal and frontal lobes (Hodges & Patterson, 2007)(See Figure 1.7). SD is primarily a disorder of conceptual knowledge and is characterised by an initial loss of understanding of the meaning of words, followed by a progressive and more universal loss of *meaning*, including for items, e.g. specific foods and faces (Hodges & Patterson, 2007; Neary et al., 1998). Though SD is characterised by language changes, individuals with SD also frequently show social impairment (Duval et al., 2012; Irish, Hodges, & Piguet, 2014).

PNFA is the least common variant of FTD and makes up around 11% of all FTLD cases (Rohrer et al., 2011). PNFA is primarily a disorder of language production, characterised by ungrammatical and laboured speech. It has been related to dorsal frontal and particularly insula atrophy and abnormality (Nestor et al., 2003; Pereira et al., 2009; Rohrer, 2012)(See Figure 1.7).

1.4.2.4 Pathology

The pathological syndrome of FTLD underlies all variants of FTD (with the likely exception of logopenic dementia, not discussed here). FTLD is associated with the pathological accumulation of protein, however it is pathologically heterogeneous and is usually caused by one of three primary pathologies (Mackenzie et al., 2010). Around 45% of FTLD cases show protein accumulations made up of tau (Rohrer et al., 2011; Shi et al., 2005). These accumulations are primarily found in one of two forms; round intraneuronal inclusions in pyramidal cells known as Pick-type inclusions, seen in 21% of FTLD cases, or neurofibrillary tangle-like structures associated with a mutation within the tau gene on chromosome 17, seen in 16% of cases (Shi et al., 2005). Most other cases of FTLD are associated with the accumulation of the DNA and RNA binding protein TDP-43, which forms small rounded or crescent shaped inclusions in the cerebral cortex (Johnson et al., 2005; Rohrer et al., 2011; Shi et al., 2005). TDP-43 is the most common cause of FTLD and accounts for up to 50% of FTLD. These TDP-43 inclusions have only been relatively recently characterised and were previously described as ubiquitin positive inclusions (Neumann et al., 2006), they are present in up to 80% of FTLD cases with ubiquitin pathology (Roeber, Mackenzie, Kretzschmar, & Neumann, 2008). The majority of the remaining cases of FTLD are associated with an accumulation of fused in sarcoma (FUS) protein (Rohrer et al., 2011; Urwin et al., 2010).

As mentioned previously, molecular pathology is not closely linked to clinical presentation in FTLD and there is not a one-to-one correspondence between pathology and presentation, indeed all of the variants of FTD are related to multiple pathologies (Shi et al., 2005) and almost all pathologies are associated with bvFTD (Hu et al., 2007; Josephs et al., 2011; Rohrer et al., 2011; Seelaar et al., 2011; Shi et al., 2005). That said, some pathologies are more specific than others. FUS pathology currently appears to be relatively selectively related to bvFTD and shows a particular relationship with very early onset cases (onset between 29 and 40 years), and in those with no family history of dementia (Rohrer et al., 2009; Rohrer et al., 2011). Similarly, some presentations seem to be more specific than others. While bvFTD is associated with almost all pathologies, SD is most commonly associated with TDP-43, and PNFA with tau pathology (Rohrer et al., 2011). Yet, on the whole, pathology appears to be relatively non-specifically related to clinical presentation. Indeed, the pathologies of FTLD are not only associated with FTD but also underlie other neurodegenerative conditions such as corticobasal degeneration, amyotrophic lateral sclerosis, and progressive supranuclear palsy (Beck et al., 2008; Hsiung et al., 2012; Josephs et al., 2006; Neumann et al., 2006; Rohrer et al., 2011). Knowledge about pathology thus provides limited specificity with regards to clinical presentation and thus an individual's prognosis or care requirements.

1.4.2.5 Genetics

Variants of many genes are associated with FTLD. While around 50% of individuals with FTD report some family history of FTLD, the proportion of individuals with a clear autosomal dominant history is around 10-27% (Rohrer et al., 2009; Seelaar et al., 2008). The C9orf72 expansion is a recently identified and common cause of familial FTD, present in around 10% of FTD cases it accounts for around 12% of cases of familial FTD (DeJesus-Hernandez et al., 2011). Individuals with C9orf72 mutations consistently show TDP-43 pathology and are Tau negative. Both between and within families, C9orf72 carriers show heterogeneity in disease duration and clinical phenotype (Hsiung et al., 2012).

Other prominent risk alleles associated with FTLD are seen in the microtubule associated protein tau (MAPT) gene and progranulin (GRN) genes. These together are seen in between 20-50% of familial cases of FTLD (Rohrer & Warren, 2011; Seelaar et al., 2011). GRN mutations are present in 12% of FTLD cases and 20% of familial FTLD cases and are associated with TDP-43 pathology (Beck et al., 2008) while mutations on the MAPT gene are responsible for tau accumulation (Poorkaj et al., 1998). As with C9orf72, there is great variability in age at onset for MAPT mutations carriers

and MAPT mutations have been associated with both behavioural and language variants of FTD as well as Parkinsonian predominant phenotypes (van Swieten & Spillantini, 2007).

While genetics are important for understanding the cause of FTD and for providing support services such as genetic counselling, genetics do not provide specific diagnostic information. Though MAPT mutations are disproportionately related to bvFTD, they have been associated with other clinical categories (Beck et al., 2008). Similarly, the clinical presentation of GRN carriers is mixed. Similar to MAPT, GRN mutations are most commonly associated with bvFTD, but they have also been associated with PNFA and corticobasal degeneration (Beck et al., 2008). Multiple clinical syndromes have also been associated with genetic mutations such as progranulin and C9orf72 (Beck et al., 2008; DeJesus-Hernandez et al., 2011; Seelaar et al., 2008). This phenotypic variability is true even in cases of autosomal dominant inheritance, family history of a specific clinical syndrome does not provide a definitive indication as to the clinical syndrome present in other members of the same family (Boxer et al., 2011; Hsiung et al., 2012; Piguet, Hornberger, Mioshi, & Hodges, 2011). Though genetics may be highly valuable for research purposes, currently they may be of limited clinical use. Half of individuals with FTD appear to be sporadic cases, with no known family history (Rohrer et al., 2009; Seelaar et al., 2008). Even in cases with a clear genetic component, as outlined, this may be of relatively limited use for specific diagnosis as mutations associated with FTLD do not directly correspond to either symptoms or diagnoses.

1.4.2.6 FTLD spectrum

Given its pathological and genetic heterogeneity, FTLD may be best thought of as a spectrum (see Figure 1.8). As previously highlighted, there is great deal of crossover between the FTD subtypes in terms of pathology, genetics and anatomical site of change (Rohrer et al., 2011). Trends are however seen in the association between patterns of degeneration and diagnostic group (Agosta, Canu, et al., 2012). As previously touched upon, the lack of direct relationship between pathology and diagnosis suggests that presenting symptoms in FTD may have more to do with the location of pathology and degeneration, than its underlying cause. Indeed the limited correspondence between pathology and symptomology in FTD has been proposed to be interpretable “as empirical proof that the *distribution* and *spread* of pathology in the brain, and perhaps not so much the *type* of pathology, dictates a patient’s clinical syndrome” (Lanata and Miller (2016), page 8). This fits with the proposal that FTD, and indeed dementias more generally, may be best conceptualised as network pathologies (Boccardi et al., 2005; Seeley et al., 2009).

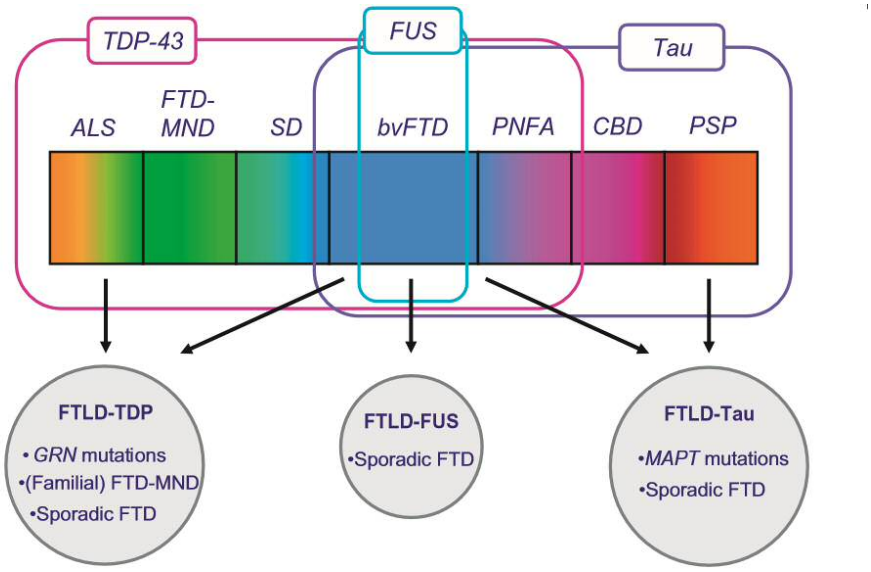

Figure 1.8. Clinical, genetic and pathological variability in Frontotemporal lobar degeneration. *Taken from (Rohrer, 2012).*

1.4.2.7 Empathy change in FTD

Profound changes in social and empathic functioning are seen in FTD, and bvFTD in particular. Indeed changes in interpersonal behaviour, including disinhibition, impaired social awareness and changes in empathy, are diagnostic features of bvFTD ("Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups," 1994; Neary et al., 1998; Rascovsky et al., 2011). Characteristic behaviours include increased selfishness (Bathgate, Snowden, Varma, Blackshaw, & Neary, 2001), failures to show concern for the distress of others (Perry et al., 2001), loss of interest in others and abnormal behaviour, such as excessive spending and theft (Lough, Gregory, & Hodges, 2001; Lough & Hodges, 2002). Socially inappropriate and unacceptable behaviour are particularly prominent in FTD with over a third of those diagnosed with bvFTD and around 27% of those with SD having been seen to exhibit criminal behaviour, including theft, sexual advances, trespass, public urination and traffic violations (Liljegren et al., 2015; Mendez, 2010). Empathy related cognitive processes may play a key role in many of these behaviours, which may be affected by an altered ability to make rational and moral decisions based on the emotions of others (Mendez, 2010; Mendez & Shapira, 2009).

Empathy change is a key yet underexplored feature of bvFTD. In the current criteria a persistent or recurrent loss of sympathy or empathy occurring within the first three years of disease onset is

one of the six diagnostic criteria for bvFTD (Rascovsky et al., 2011)(See Table 1.1), three of which are necessary for a diagnosis. Yet, despite its importance in bvFTD, there remains relatively little direct research of the nature of empathy change in FTD (Baez et al., 2014; Rankin, Kramer, & Miller, 2005), of the work which has, the majority has focused on empathy change in FTD has utilised questionnaire based informant reports of empathic behaviour change. Such work has consistently found that individuals with FTD have decreased levels of both cognitive and affective components of empathy in the form of reduced mental perspective taking and empathic concern (Eslinger, Moore, Anderson, & Grossman, 2011; Lough et al., 2006; Rankin et al., 2006; Rankin et al., 2005; Davis, 1980). This questionnaire-based work is supported by studies that have utilised performance-based neuropsychological assessments. Outlined below.

Primary Symptom	Characteristic symptoms
Early Behavioural Disinhibition*	• Socially inappropriate Behaviour • Loss of Manners or decorum • Impulsive, careless actions
Early Apathy*	• Apathy • Inertia
Early Loss of sympathy or Empathy*	• Diminished response to the needs and feelings of others • Diminished social interest and personal warmth
Early Stereotyped or ritualistic behaviour*	• Simple repetitive movements • Compulsive or ritualistic behaviour • Stereotypy of speech
Hyperorality & Dietary change	• Altered food preferences • Binge eating or increased consumption of alcohol or cigarettes
Executive deficits with relative sparing of memory and visuospatial functioning	• Executive deficits • Relative sparing of episodic memory • Relative sparing of visuospatial skills

Table 1.1 Behavioural or Cognitive symptoms of bvFTD according to Rasckovsky et al 2011. At least one characteristic symptom must be present for relevant symptom to be classified as present. **Occurring in the first three years of disease*

1.4.2.7.1 Cognitive empathy

Individuals with bvFTD show an impaired ability to mentalise using a range of tests (Eslinger et al., 2007; Lough & Hodges, 2002), including assessments of comprehension of insincere communication (Shany-Ur et al., 2012), false belief tasks (Freedman, Binns, Black, Murphy, & Stuss, 2013; Gregory et al., 2002; Torralva et al., 2007) and assessments that involve making mental state inferences from cartoons (Lough et al., 2006; Snowden et al., 2003). Individuals with bvFTD further show a loss of embarrassment (Bathgate et al., 2001; Sturm, Ascher, Miller, & Levenson, 2008), suggesting that they may be unaware of the social judgements of others. Indeed it has been suggested that the social cognitive deficits in bvFTD may be due primarily to deficits in mentalising (Bora, Walterfang, & Velakoulis, 2015; Gregory et al., 2002; Henry, Phillips, & von Hippel, 2014; Kipps & Hodges, 2006).

1.4.2.7.2 Perceptual empathy

Assessments have consistently shown the presence of deficits in emotion perception and decoding in bvFTD. Deficits are seen with emotion perception from static faces (Janine Diehl-Schmid et al., 2007; Kumfor & Piguet, 2012; Lough et al., 2006; Oliver, Virani, Finger, & Mitchell, 2014; Rosen et al., 2002), voices (Keane, Calder, Hodges, & Young, 2002; Shany-Ur et al., 2012; Snowden et al., 2008), bodies (Van den Stock et al., 2015), eyes alone (Gregory et al., 2002; Oliver et al., 2014; Snowden et al., 2008; Torralva et al., 2007) and dynamic faces and bodies (Van den Stock et al., 2015). Interestingly this is despite maintained emotional reactivity to emotional stimuli, such as happy, sad or scary films (Werner et al., 2007) and despite an apparently intact ability to make other types of perceptual discriminations from the stimuli, such as between facial identities (Couto et al., 2013; De Winter et al., 2016; Keane et al., 2002; Rosen et al., 2002). A review of such work revealed that such impairments in emotion perception are consistent across studies and across displayed emotions (Kumfor & Piguet, 2012).

1.4.2.7.3 Motor empathy

In line with the difficulties of assessing motor empathy, as outlined previously, limited work has investigated motor empathic functioning or mirroring in bvFTD. Studies that have addressed aspects of motor empathy, usually intertwined with assessments of other aspects of empathy, have however suggested that impairments are present in motor empathy. When presented with images of realistic situations, individuals with bvFTD show an impaired ability to answer questions

on how others feel and report reduced levels of concern or mirroring of emotion (Oliver et al., 2015). Concerning pain, one paper showed that when presented with images of others in pain, levels of empathic concern were reduced in individuals with bvFTD and deficits were seen in inferring the intentions of those causing pain, particularly when it was unintentional (Baez et al., 2014). Such work is consistent with impaired motor empathy, however the confounding of the results with other components of empathy (in particular cognitive empathy) makes it hard to draw conclusions from such work.

1.4.3 White matter change in bvFTD

FTD may facilitate the study of the network structure underpinning empathic functioning thanks to its particular impact on brain white matter. While imaging work has tended to focus on grey matter atrophy, histology work has shown that changes to white matter may have in important role in FTD. Protein accumulation (Neumann et al., 2007; Neumann et al., 2009) and changes to glial cells (Schofield, Kersaitis, Shepherd, Kril, & Halliday, 2003) have been seen in FTD, not only in grey matter but also in white matter. For example pathological changes have been seen in oligodendrocytes (Neumann et al., 2007), cells that provide support and insulation for neurons and speed the transmission of neural signals. Degeneration of these cells may impair signal transmission and thus intercommunication between dispersed brain regions, potentially independently of any degeneration of functional brain areas. Such white matter changes may have an important role in network functioning.

A substantial body of evidence describes the cortical regions of atrophy in FTD, though relatively less focus has been paid to white matter alteration. The detection of gross atrophy is of importance for both research and diagnosis as clinical criteria require evidence of neurodegeneration for the diagnosis of probable FTD (Neary et al., 1998; Rascovsky et al., 2011). Across FTD, significant grey matter atrophy is seen in the orbitofrontal cortex, dorsolateral frontal cortex, ACC, Anterior insula, ATL and thalamus (Borroni et al., 2007; Whitwell et al., 2012; Zhang et al., 2011). On the whole, white matter change in bvFTD has been reported to mirror patterns of grey matter loss. Significant change is seen in tracts such as the anterior CB, anterior corpus callosum (CC) and the UF, which lie along or connect regions of grey matter atrophy (Agosta, Canu, et al., 2012; Mahoney et al., 2014; Matsuo et al., 2008; McMillan et al., 2012; Whitwell et al., 2010; Zhang et al., 2011; Zhang et al., 2009; Zhang et al., 2013).

Though most work as focused on grey matter change, white matter may in fact be the initial sight of structural change in FTD. Though white matter change boardering grey matter change could indicate that white matter degeneration is due to spreading of grey matter pathology, it seems unlikely that is the case. For example, though evidence is still inconclusive, histology work has indicated that there may be a selective degeneration of Von-Economo neurons (VEN) early in FTD (Kim et al., 2012; Santillo, Nilsson, & Englund, 2013; Seeley et al., 2006). VEN or 'spindle cells' are a type of large bipolar neuron, characterised by their large and elongated cell body (Allman, Hakeem, & Watson, 2002; Nimchinsky, Vogt, Morrison, & Hof, 1995). These cells are found primarily in the fronto-insular cortex and ACC (Allman, Watson, Tetreault, & Hakeem, 2005; Butti, Santos, Uppal, & Hof, 2013) though they have also been identified in the mPFC (Fajardo et al., 2008) and run through the anterior CB (Allman et al., 2010; Nimchinsky et al., 1995). These cells are rare at birth but proliferate in number during the first 8 months of life, reaching adult levels by 4 years of age (Allman et al., 2010). The regions in which VEN are found are some of the areas which degenerate at the earliest stages of FTD (Seeley et al., 2008), leading some to propose that the presence of VEN may render these regions selectively vulnerable to FTD pathology (Seeley, 2008).

In line with evidence from histological studies, imaging work has corroborated the early degeneration of white matter in FTD. White matter appears to be disporportionately affected early on in FTD relative to other forms of dementias such as AD (Zhang et al., 2011) and to show a faster rate of atrophy over time relative to both grey matter in the same individuals and white matter in AD patients (Frings et al., 2014). Those with a genetic pre-disposition to FTD but without apparent symtpoms also appear to have white matter abnormalities (Dopper et al., 2013), which appear to increase over time, despite no apparent abnormalities in grey matter (Dopper et al., 2013). Imaging has further shown that, consistent with white matter change potentially occurring prior to grey matter change, white matter degeneration may extend beyond the areas of grey matter change (Agosta, Canu, et al., 2012; Borroni et al., 2007), suggesting that white matter degeneration may not simply follow grey matter atrophy. White matter microstructural change as assessed using DWI has further been seen to be more severe than grey matter atrophy (Agosta et al., 2015) and may be the imaging metric most sensitive to the presence of FTD (McMillan et al., 2014), supporting the suggestion that white matter may have a central role in FTD.

In comparison to other FTD sub-types, bvFTD has in particular been associated with profound white matter change (Agosta et al., 2015; Lu, Mendez, et al., 2013). In bvFTD, particular

degeneration is seen in prefrontal and temporal white matter tracts (Lillo, Mioshi, Burrell, et al., 2012; Zhang et al., 2013). Both whole-brain and tract-based analysis methods show the presence of altered white matter in frontal and temporal white matter pathways including the CC, CB and UF (Zhang et al., 2011; Zhang et al., 2009). White matter pathology is, however, not solely confined to frontal regions as whole brain analyses show widespread changes with alterations apparent in even parietal white matter (Zhang et al., 2009). Indeed in a tract-by tract analysis of white matter change, all 21 tracts investigated were seen to significantly differ between healthy adults and individuals with bvFTD, those with bvFTD having altered DTI metrics such as lower FA (Daianu et al., 2016). While alterations were also seen in all 21 tracts in individuals with early onset AD, significantly greater abnormalities were seen in bvFTD, supporting the proposal that white matter alteration may be an early change in bvFTD, but occur relatively later on in AD. DWI thus has shown white matter alteration to be a prominent feature of bvFTD.

White matter change seems like a possible candidate for mediating early social cognitive changes in bvFTD both thanks to the early occurrence of white matter pathology in FTD and to the posited function of VEN. Whilst VEN were first identified and characterised in humans, they have subsequently been identified in great apes (Allman et al., 2010), elephants (Hakeem et al., 2009), and large cetaceans such as Humpback whales (Hof & Van der Gucht, 2007) and bottle nosed dolphins (Butti, Sherwood, Hakeem, Allman, & Hof, 2009). The complex and highly social nature of these species has led to VEN to be associated with social functioning (Allman et al., 2010; Butti et al., 2013). If VEN indeed selectively support social functioning then this would indicate that the potentially selective degeneration of VEN in bvFTD (Kim et al., 2012; Santillo, Nilsson, et al., 2013; Seeley et al., 2006), and consequent white matter change, may have a key role in social cognitive impairment in bvFTD.

1.4.4 Sites of white matter alteration in bvFTD

Evidence of early change in both empathic functioning and white matter in bvFTD suggests that the white matter pathways that show early alteration in bvFTD may be strong candidates for those that have a key role in supporting empathic networks in the healthy brain. To identify these pathways we first need to identify those white matter pathways that show substantial alteration in bvFTD. Despite the body of literature showing the presence of white matter alteration in FTD, there are currently no prominent meta-analyses or systematic reviews of this literature to

highlight the white matter pathways consistently altered in bvFTD. Therefore, here, a systematic review of the literature is reported which was undertaken to highlight the white matter pathways seen to most consistently be altered in bvFTD, particularly early in disease progression.

The initial search for the systematic review was carried out on the 12th of February 2014. Searches were carried out for research papers that were written in English and reported data on atrophy or alteration of white matter in individuals with bvFTD, a genetic predisposition to FTD, or undifferentiated FTD. Only published research papers were included, conference abstracts and reviews were not considered. Studies must have been carried out using DWI, those using voxel based morphometry were not included as it has previously been shown to be relatively insensitive to white matter pathology (Buchel et al., 2004; Whitwell et al., 2005). Searches were carried out in PubMed and Web of Science using the search terms: *diffusion tensor imaging, diffusion magnetic resonance imaging, DTI or white matter and frontotemporal dementia, frontotemporal lobar degeneration, FTD, FTLD or bvFTD.* 126 articles were identified through PubMed and 196 articles through the Web of Science. The abstracts of each of these articles were reviewed to determine which articles were relevant for inclusion in the systematic review. Only articles in which individuals with FTD were compared to controls were included. From the PubMed search, 30 articles were identified as including information about white matter, of these, 13 were identified as including DWI data looking at either the whole brain or multiple tracts. 3 included tract of interest analysis. Of the studies two studies reported only individuals at genetic risk for FTD. Two studies were identified that only looked at specific tracts - the CC and CB and these studies are not reported here (Bozzali et al., 2013; Santillo, Mårtensson, et al., 2013). 20 articles were identified through the Web of Science search, all of which were also identified through PubMed.

Across the studies, white matter alteration was seen across predominantly frontal and temporal regions (see Table 1.2). Four studies reported only sites of change at a lobar level, reporting alteration across frontal and temporal lobes (Agosta, Scola, et al., 2012; Chen et al., 2009; Hornberger, Geng, & Hodges, 2011; Zhang et al., 2011). Of the remaining nine, six reported alteration in the UF and CC while five reported alteration in the CB. Most other tracts were reported in fewer than half of the cases (see table 1.2).

	Participants	Acquisition	Analysis	Sites investigated	Site of alteration
Zhang et al., 2013	bvFTD (13) HC (6)	4 Tesla 6 directions	Whole brain, ROI, Tractography	a/pCC, a/pCB, UF, AF, Fx	a/pCC, aCB, UF, Fx
Zhang et al., 2009	FTD (18) HC (18)	4 Tesla 6 directions	Whole brain, Tractography	a/pCB, UF, a/pCC, CST	aCC, aCB, pCB, UF
Matsuo et al., 2008	FTD (20) HC (17)	1.5 Tesla 15 directions	Tractography	aCC, pCC, AF, UF, ILF	aCC, AF, UF, ILF
Chen et al., 2009	FTD (7) HC (20)	1.5 Tesla 25 directions	ROI	Frontal, Parietal, Temporal	Temporal, Frontal,
Whitwell et al., 2010	bvFTD (16) HC (19)	3 Tesla 21 directions	ROI	UF, CST, a/pCB, SLF, a/pILF, a/pCC	UF, aCB, aILF, SLF,
Lillo et al., 2012	bvFTD (15) HC (18)	3 Tesla 32 directions	TBSS		Fm, aCC, aILF, CST
Mahoney et al., 2014	bvFTD (27) HC (20)	3 Tesla 64 directions	TBSS		UF, CB, CC, SLF, ILF, ATR, CST
Agosta et al., 2012	bvFTD (13) HC (25)	3 Tesla 32 directions	TBSS		Frontal & Temporal
Zhang et al., 2011	bvFTD (20) HC (21)	4 Tesla 6 directions	Whole brain		Frontal & Temporal
Hornberger et al., 2011	bvFTD (14) HC (18)	3 Tesla 32 directions	TBSS		Frontal & anterior Temporal
Borroni et al., 2007	fvFTD (28) HC (23)	1.5 Tesla 6 Directions	ROI	SLF, ILF, IFOF	SLF
*Dopper et al., 2013**	MAPT/GRN (37) HC (38)	3 Tesla	TBSS		UF, SLF, ILF, sCR, EC, Fm, IFOF, pCC
*Pievani et al., 2014**	GRN (5) HC (5)	1.5 Tesla 30 directions	Whole brain		SLF, CB, CST,

Table 1.2. Sites of altered white matter in behavioural or frontal variants of frontotemporal dementia.

ROI=Region of Interest analysis; TBSS=Tract based spatial statistics; ATR=anterior thalamic radiation; sCR=superior corona radiata; UF=Uncinate fasciculus; a/pSLF=anterior/posterior superior longitudinal fasciculus; CST=corticospinal tract; IFOF=inferior fronto-occipital fasciculus; a/pCC=anterior/posterior corpus callosum; EC=external capsule; a/pCB= anterior/posterior cingulum bundle; Fm=forceps minor; Fx=fornix; a/pILF=anterior/posterior inferior longitudinal fasciculus; AF=arcuate fasciculus; SLF= superior longitudinal fasciculus. ** Report involving individuals at genetic risk.*

OF the white matter structures seen via the systematic review, the UF and the CB were selected for further consideration. Both the UF and the CB are strong candidates for playing a role in social cognitive functioning as both provide connectivity within the limbic system, a system commonly associated with social cognitive functioning (Catani, Dell'Acqua, & Thiebaut de Schotten, 2013). Indeed evidence indicates that alterations to the UF may be related to functional changes in individuals with FTD (Hornberger et al., 2011). Though the exact function of this pathway is largely unknown, it is generally thought to be important for social and emotional processing (Von Der Heide, Skipper, Klobusicky, & Olson, 2013). The UF and CB, are therefore focused upon in chapters 2 and 3 of this thesis respectively.

Little work has focused on longitudinal changes in white matter and so it is not possible to be certain of whether the tracts of interest (UF and CB) are those that alter earliest in bvFTD. Existing longitudinal work has however reported white matter alteration, using TBSS, in frontal and temporal regions (Frings et al., 2014; Lam, Halliday, Irish, Hodges, & Piguet, 2014) and highlighted CB and UF as structures potentially prominently altered early on (Lam et al., 2014). The strongest evidence for early alteration of these pathways is the presence of alteration to both fascicles in asymptomatic individuals with genetic risk for FTD (Dopper et al., 2013; Pievani et al., 2014). Both tracts also show sensitivity to the presence of disease and have been highlighted as valuable for discriminating individuals with bvFTD from healthy adults (Agosta, Scola, et al., 2012; Mahoney et al., 2014; Santillo, Mårtensson, et al., 2013). Indeed alteration to the anterior CB has previously been described as a hallmark feature of bvFTD (Lillo, Mioshi, Burrell, et al., 2012).

1.5 BvFTD as a clinical model for neurocognitive network based changes in empathic functioning

As discussed previously, it is a well established principle of neurology and neuropsychology that we can learn about functioning through studying individuals who have structural or functional pathology. Studying clinical groups can thus provide an insight into how neurocognitive networks underpin complex social behaviour by providing evidence for a relationship between perturbation to specific neural networks and social cognitive change. Considering the behaviour of individuals with localised damage can further provide insight into the nature of broader behavioural change, allowing research to investigate beyond specific cognitive abilities and consider the role of specific cognitive functions in everyday behaviour.

Though the presence of a profound deficit in social cognitition, including empathy, in bvFTD is well established, there is a relative derth of work that has considered what we may learn about social or empathic functioning through the lens of bvFTD.

1.5.1 Dissociations between networks

BvFTD may selectively affect the neurocognitive networks that underpin key components of empathic functioning. If these networks are indeed dissociable it is feasible that, early on in disease progression, some components of empathic functioning may show more profound deficits than others. While dissociations between cognitive abilities or relationships between neural structure and cognitive function can be investigated in healthy adults, such work does not necessarily provide evidence that functions are underpinned by separable neurocognitive networks. When associations or dissociations are merely correlational, as in work with healthy adults, it is always feasible that any observed correlations are mediated by other variables. Studying groups such as individuals with bvFTD, who are known to have neural alteration, can provide key evidence of causal relationships between structural perturbation and cognitive change, or evidence for a neural dissociation between cognitive functions. Studying empathic cognition in individuals with bvFTD may, therefore, provide evidence for the presence and dissociation of cognitive components of empathy and their underpinning of neurocognitive networks.

1.5.2 The nature of behavioural change in FTD

'Important problems emerge when researchers rely on overly simplified models of any complex psychological phenomenon for too long.'

Zaki & Ochner 2012

Empathic functioning is complex, dynamic, interpersonal and context dependent, therefore to understand how changes in cognitive functions relate to behaviour it is important to consider complex behaviours such as empathy in their natural context. Considering the nature of complex behaviours, as a whole, in their natural setting, is critical. Studying cognitive sub-processes in simplified and artificial contexts gives us a view of only a small section of broader and more complex functions. By utilising questionnaires and behavioural tasks, questions about frequency or

severity of behavioural changes can be asked (Baez et al., 2014; Eslinger et al., 2011; Oliver et al., 2015; Rankin et al., 2005) but they remain, by their nature, reductionist. The necessary operationalisation of complex and subtle abilities that occurs in the production of standardised quantitative measures results in an artificial narrowing of the functions being investigated, which are separate from the natural every day behaviours generally described as empathic.

There is a surprisingly limited consideration of everyday behaviour in bvFTD within the literature. This is despite the fact that to reach a diagnosis, doctors must hear and consider detailed descriptions of behavioural symptoms given by individuals with FTD or their families. Beyond relatively brief clinical case reports of patient behaviour (Lough et al., 2001; Lough & Hodges, 2002; Mendez & Shapira, 2009), the bvFTD literature tends to report quantitative assessments of behaviour and numerical indices of performance on social tasks (Baez et al., 2014; Kumfor et al., 2014; Lough et al., 2006). These methods have established the presence of functional changes in domains such as mentalising (Eslinger et al., 2007; Lough & Hodges, 2002; Lough et al., 2006; Shany-Ur et al., 2012; Snowden et al., 2003), emotion perception (Janine Diehl-Schmid et al., 2007; Keane et al., 2002; Gregory et al., 2002; Shany-Ur et al., 2012) and self-conscious emotions (Bathgate et al., 2001; Sturm et al., 2008) but provide limited discussion of the everyday social and empathic behaviour change that occurs in bvFTD. Even published case reports give little detail on social and interpersonal behaviour, especially in a family context, even when other behaviours are described in detail (Lough & Hodges, 2002). Nor are reports of altered functioning on cognitive assessments such as the faux pas recognition task contextualised with descriptions of the individual's day-to-day behavioural changes (Lough & Hodges, 2002). Those reports that are present within the literature from family members tend to be in the form of responses to prescriptive questionnaires (Eslinger et al., 2011; Fernandez-Duque, Hodges, Baird, & Black, 2010; Oliver et al., 2015), limiting the scope of interpretations that can be made.

Within the current literature there is minimal consideration of what the breakdown of everyday social behaviour in bvFTD may tell us about how empathic cognition operates in daily social interactions. The study of bvFTD may however be able to tell us a great deal about the behavioural impact of changes to empathic neurocognitive systems. Such observations are only possible in the context of neural alteration, as low cognitive performance in the general population may be due factors such as social experience, which many simultaneously impact on other features of behaviour. Only in cases of acquired damage can we presume that unusual behaviours or behavioural change are due to impaired neurocognitive functioning (Beer et al., 2003).

Few studies have investigated naturalistic empathic behaviour in bvFTD in an ecologically valid context. Most work has instead used controlled experimental tasks (as described above) or questionnaire based reports of empathic behaviour. One commonly used questionnaire is the interpersonal reactivity index (IRI) (Davies, 1980). The IRI utilises questions that tap into four putative components of empathic functioning, Perspective taking, Fantasy, Empathic concern, and personal distress, two of which broadly assess cognitive and affective components of empathy, respectively (Davies, 1980). To assess empathic behaviour in bvFTD the IRI is scored by a knowledgeable informant due to the limited insight of individuals with bvFTD (O'Keeffe et al., 2007). The IRI thus captures some aspects of the interpersonal nature of empathic functioning and has been used to show impairments in both cognitive and affective components of empathy in bvFTD (Eslinger et al., 2011; Rankin et al., 2006; Rankin et al., 2005). Yet, as with other questionnaire-based reports the IRI provides little information regarding the nature of the everyday behaviours of individuals with bvFTD as it is prescriptive and only allows informants to report on behaviours that are already included in the questionnaire.

Behavioural tasks address some of the issues present in questionnaires but still fail to capture naturalistic everyday behaviour. Behavioural tasks allow for questions regarding specific cognitive domains to be explored and allow researchers to control for cognitive functions that are not of interest, such as verbal fluency. Yet they suffer from considerable issues regarding their ecological validity. Though some tasks, such as the Awareness of Social Inference Test (TASIT), have been developed to incorporate complex naturalistic stimuli (e.g. videos) into neuropsychological assessment (McDonald, Flanagan, Rollins, & Kinch, 2003), many do not. Most, further lack ecological validity by using closed and unnatural questioning and by being administered in artificial study environments. Many tasks also fail to incorporate ongoing and interactional features of social behaviour such as social context or relationship dynamics, known to influence social processing (Baez et al., 2017; Matsui et al., 2016; Melloni, Lopez, & Ibanez, 2013; Samur, Lai, Hagoort, & Willems, 2015). These dynamic features of social behaviour are hard (if not potentially impossible) to systematically incorporate into assessments, partly because it remains poorly understood how they influence behaviour (Bernhardt & Singer, 2012; Decety, 2010, 2011; Singer et al., 2006; Zaki & Ochsner, 2012). Such features may therefore be intentionally removed from experimental tasks, being hard to bring into the laboratory setting and hard to experimentally manipulate. Thus, despite attempts to develop more sensitive and accurate assessments of empathic functioning (Spreng, McKinnon, Mar, & Levine, 2009), there remain few, if any, reliable,

theory bound, comprehensive assessments of empathic functioning and behaviour (Kanske, Böckler, Trautwein, & Singer, 2015). As such there remains a need for new tasks or ways to evaluate empathy (Decety, 2011).

1.5.2.1 Qualitative methods in empathy research

The study of the nature of everyday behaviours in bvFTD may benefit from a hypothesis free, qualitative approach, which is open to all results and is unconstrained by expectation as to what will be found. A major strength of qualitative research is that it captures a phenomena holistically and in context. This approach also allows for the consideration of the interactive nature of social behaviour, something that is hard to incorporate in controlled and quantitative studies. Further to this, unlike quantitative research, qualitative work does not require domains of interest to be established before research begins, rather, the data itself determines what is of relevance (Charmaz, 2006). This is of value for considering empathic functioning as altered empathic behaviour could be due to change in a whole host of cognitive functions, which to investigate fully could require vast batteries of tasks using quantitative methods.

Qualitative data is valuable in addition to quantitative data. Qualitative data regarding how individuals perform neuropsychological assessments can improve the ability to discriminate between those with FTD and AD (Thompson, Stopford, Snowden, & Neary, 2005). Qualitative methods also enable researchers to obtain the perspective of individuals with whom individuals with FTD regularly interact. This is important for considering social behaviour, which is intrinsically interpersonal. Such reports may further be of relevance for in bvFTD as it is generally family members, not patients themselves that highlight the presence of social changes. Loss of insight is a frequent and early symptom of FTD and as such those affected often report themselves as having normal empathic behaviour, despite family members rating them as significantly impaired (Eslinger et al., 2011; Hsieh, Irish, Daveson, Hodges, & Piguet, 2013). Capturing the nature of the behaviours that lead family members to feel that their relative shows altered empathy may provide us with greater insight into the cognitive changes underpinning social behavioural changes and why these changes are so burdensome to families.

A qualitative approach is inductive and hypothesis forming. Qualitative work may therefore additionally have value for developing future quantitative assessments of empathic functioning and bvFTD.

1.6 Research questions and chapters

In this thesis I will explore distinct components of empathic functioning at the brain network-level. I will take a novel mixed methods approach to consider empathic functioning at a neural, cognitive and behavioural (interpersonal) level and will consider FTD as a clinical model of empathic network neurodegeneration (Seeley et al., 2012). Firstly, I will investigate the neural underpinnings of empathic functioning in healthy adults by investigating the relationship between white matter microstructure, in tracts that provide connectivity between cortical regions established to have a role in perceptual and cognitive empathy, and cognitive components of empathic functioning. In this work I adopt an individual differences approach in healthy adults (Yovel, Wilmer, & Duchaine, 2014). This work will be guided and informed by a consideration of bvFTD, which, early in disease progression, may preferentially affect white matter pathways (Frings et al., 2014; Lam et al., 2014; Seeley, 2008; Seeley et al., 2006; Zhang et al., 2011). Secondly I will consider the behavioural impact of perturbations to the networks underlying empathic functioning by considering the cognitive and behavioural changes in empathic functioning observed in FTD, a neurodegenerative disease that selectively affects neural networks associated with social and empathic functioning (Agosta, Scola, et al., 2012; Boccardi et al., 2005; Cerami et al., 2014). Considering empathic functioning from a neural to a behavioural level this work will incorporate neuroimaging, neuropsychology and the qualitative study of complex interpersonal social behavioural change in FTD.

In chapters 2 and 3, I will investigate empathic functioning at a neural network level. These chapters investigate the central role that network connectivity may play in supporting empathic processing by exploring the relationship between individual differences in performance on social cognitive tasks assessing perceptual and cognitive components of empathic functioning and white matter microstructural properties of key white matter fibre tracts. Tract selection was based on the systematic review reported here, indicating an early alteration in the UF and CB in bvFTD. The selection of cognitive functions of interest was informed by existing evidence regarding the cognitive and neural structure of empathy and functional change in bvFTD. The purpose of this work was to determine whether in healthy adults there is evidence for these white matter pathways (UF and CB) being related to functioning on two components of empathic functioning (emotion decoding and mentalising) via evidence of selective relationships between the

microstructure of these white matter pathways and individual differences in performance on empathy relevant tasks.

In chapters 4 and 5, I will consider the nature of empathic functioning in bvFTD. In chapter 4 I will consider bvFTD as a model of social cognitive network breakdown and present a neuropsychological single case study testing the putative dissociation between perceptual and cognitive components of empathic functioning. Chapter 4 utilises the tasks from Chapters 2 & 3 providing converging evidence for a dissociation between neurocognitive networks underlying the two posited components of empathy. This work will additionally utilise a novel naturalistic assessment of story-based mentalising, and present evidence for the value of this task for the study of bvFTD. Chapter 5 will move beyond the consideration of cognitive components of empathic functioning to explore changes in complex everyday empathic functioning that occur as a result of FTD. Qualitative methods will be used to obtain the perspective of family members of individuals with FTD on their relative's social behaviour. This chapter will attempt to address the challenge of capturing the broad nature of empathic functioning and explore it in a naturalistic context. In this chapter I will consider the insight that may be gained through qualitative methods into the interactional nature of social and empathic functioning which is not readily accessible through quantitative study of healthy adults. I will provide a richly detailed account of behavioural changes experienced by family members with a view to considering what such behaviours may tell us about the underlying cognitive changes that may result in changed empathy in bvFTD.

The results of this work will be summarised and brought together in the general discussion. Here I will consider what this work and a multi-methods approach more generally, may bring to the study of empathic functioning. I will bring together the findings of the four experimental chapters to consider what these different approaches together may tell us about empathic functioning in general and specifically about the nature of its change in bvFTD. I will consider how these insights may direct future work and the development of cognitive assessments which may help improve our understanding of bvFTD and its diagnosis. I will finally suggest a novel direction for future research wherein development and degeneration may be meaningfully considered in parallel, and propose that future work should undertake a parallel consideration of bvFTD and ASD. I will present an argument for how such work may further our understanding of the neurocognitive underpinnings of empathic functioning and social cognitive functioning more widely.

2

Frontal white matter may support neurocognitive networks for emotion: A role for the uncinate fasciculus in facial emotion decoding

2.1 Introduction

In humans, the face is the primary canvas used to express emotions nonverbally (Ekman, 1965). Given that human social interactions are replete with emotional exchanges, facial emotion processing abilities are crucial for the regulation of interpersonal relationships and for social functioning more generally (Fischer & Manstead, 2008). As such, facial emotion processing is a critical mechanism for responding to others empathically and modifying behaviour based on the cognitive or emotional state of others (Matsumoto, Keltner, Shiota, O'Sullivan, & Frank, 2008). In line with this, individual differences in the ability to decode facial expressions are linked to several determinants of social success, such as the ability to effectively negotiate (Elfenbein, Foo, White, Tan, & Aik, 2007; Momm et al., 2015; Woolley, Chabris, Pentland, Hashmi, & Malone, 2010).

Face processing has been associated with a network of grey matter regions (Fusar-Poli et al., 2009; Tsao, Schweers, Moeller, & Freiwald, 2008). Emotion expression processing in particular has been associated with fronto-temporal brain regions, including the amygdala and ventromedial prefrontal cortex (vmPFC) (Adolphs, 2002; Willis, Palermo, McGrillen, & Miller, 2014). Given the dynamic and complex nature of social interaction, it is plausible that the rapid decoding of facial expressions requires the efficient transfer of information between such distributed temporal and frontal cortical regions (Adolphs, 2002). As white matter tracts are the brain structures that allow such efficient, synchronised transfer of information across distant brain regions (Fields, 2008). The structure of these tracts will influence the ability of distant regions to intercommunicate. As such,

these tracts may be critical for performance on tasks that challenge this critical domain of social-emotional functioning.

The UF is a hook-shaped cortico-cortical white matter pathway that provides bidirectional connectivity between the orbital and medial prefrontal cortex (OMPFC), and anterior portions of the temporal lobe (ATL), including the temporal pole (TP), perirhinal cortex and amygdala (Petrides & Pandya, 2007; Schmahmann et al., 2007; Thiebaut de Schotten et al., 2012). By virtue of its connectivity, the UF has been suggested to underpin a 'temporo-amygdala-orbitofrontal network' (Catani et al., 2013) or 'anterior temporal system' (Ranganath & Ritchey, 2012), potentially critical to the regulation of social and emotional behaviour (Von Der Heide et al., 2013). Work in nonhuman primates originally identified the anterior temporal and prefrontal cortical areas as being important in the control and regulation of social behaviour (Franzen and Myers, 1973; Kling and Steklis, 1976; Brothers, 1990; see Machado and Bachevalier (2006) for later refinements). This was that supported by subsequent neuropsychological investigations in humans which found that damage to both ATL (including amygdala) (Adolphs, Tranel, & Damasio, 2001; Adolphs et al., 1999; Anderson, Spencer, Fulbright, & Phelps, 2000; Cancelliere & Kertesz, 1990; Schmolck & Squire, 2001) and OMPFC (Dal Monte et al., 2013; Heberlein, Padon, Gillihan, Farah, & Fellows, 2008; Hornak, Rolls, & Wade, 1996; Tsuchida & Fellows, 2012) are associated with impaired facial emotion decoding, particularly when RH ATL and OMPFC were damaged (Adolphs, 2002), particularly for negative, relative to positive, valence emotions (Adolphs et al., 2001). This suggests that this network may have a key role in facial emotion decoding, yet the precise functions of this network are unclear.

In bvFTD the decoding of facial expressions of emotions is a prominent domain of functional alteration (Janine Diehl-Schmid et al., 2007; Keane et al., 2002). Deficits have been seen across a range of tasks including the Ekman faces (Janine Diehl-Schmid et al., 2007; Keane et al., 2002), emotional hexagon (Buhl, Stokholm, & Gade, 2013), TASIT (Kipps, Nestor, Acosta-Cabronero, Arnold, & Hodges, 2009; Shany-Ur et al., 2012) and The Reading the Mind in the Eyes Test (RMET) (Bora et al., 2015; Gregory et al., 2002; Torralva et al., 2007; Torralva, Roca, Gleichgerrcht, Bekinschtein, & Manes, 2009). While some have argued that apparent impairments may be due to difficulties in facial perception (Freedman et al., 2013), reports of a preserved ability to identify familiar faces (Keane et al., 2002) and to discriminate between facial identities (Couto et al., 2013; Rosen et al., 2002) makes this seem unlikely. Supporting a likely specificity to facial emotion

deficits, work has further shown that facial emotion perception deficits are not due to impaired attention, or specifically due to an inattention to diagnostic facial features (Oliver et al., 2014). Evidence is thus consistent with a specific deficit in facial emotion decoding being present in bvFTD.

In the systematic review presented in the introduction chapter, the UF was identified as a common site of alteration in bvFTD and as being sensitive to disease presence and progression (Mahoney et al., 2014; Matsuo et al., 2008). In concert with the presence of facial emotion processing deficits this could indicate that the UF has a role in supporting facial emotion processing. Consistent with this proposal, disruption of the UF is not only seen in FTD (Mahoney et al., 2014; Whitwell et al., 2010), but also in a range of neurological and psychiatric conditions that are characterised by altered social behaviour and facial emotion processing, including ASD (Kumar et al., 2010; Pugliese et al., 2009), psychopathy (Craig et al., 2009; Sundram et al., 2012), and social anxiety disorder (Baur et al., 2013; Phan et al., 2009).

Here, in healthy young adults I test this specific hypothesis that the UF has a critical role in the decoding of facial expressions of emotion. Such a relationship between UF structure and facial emotion processing is indicated by preliminary neuropsychological work which has shown lesions impacting, but not selective to, the UF can lead to impaired facial emotion recognition (Fujie et al., 2008; Mike et al., 2013; Oishi et al., 2015). The role of the UF in facial emotion processing has however yet to be systematically investigated as little work has considered the role that white matter may play in supporting facial emotion processing, particularly in healthy adults. Here, across two separate experiments, I utilised an individual differences approach (Yovel et al., 2014) to isolate the functional contribution of the UF to the decoding of facial emotion expression in healthy adults.

In Experiment 1, participants completed the RMET (Baron-Cohen et al., 2001), a well-established task which requires participants to select a verbal label that best describes the mental state being expressed in a series of images of the eye region of the face. While initially developed for use in ASD, the RMET is a valid and sensitive measure of subtle individual differences in facial emotion processing in healthy individuals (Baron-Cohen et al., 2001; Vellante et al., 2013). Deficits in performance on the RMET have been reported in FTD (Baez et al., 2014; Baron-Cohen et al., 1997; Baron-Cohen et al., 2001; Gregory et al., 2002; Torralva et al., 2007; Torralva et al., 2009) and

other conditions associated with UF abnormalities, including ASD (Baron-Cohen et al., 2001) and psychopathy (Ali & Chamorro-Premuzic, 2010). Further to this, previous work has shown RMET performance to be sensitive to focal lesions of both the ATL and the OMPFC (Adolphs, 2002; Adolphs, Baron-Cohen, & Tranel, 2002; Shaw et al., 2005). Participants in Experiment 1 also completed an 'odd-identity-out' test of facial identity discrimination to control for non-emotional facial perceptual ability (Hodgetts et al., 2015). In Experiment 2, a separate group of participants completed the RMET and the odd-identity-out task, as well as an 'odd-expression-out' test of facial emotion discrimination (Palermo, O'Connor, Davis, Irons, & McKone, 2013), analogous to the odd-identity-out task, which eliminated the linguistic requirements of the RMET.

To isolate the role of UF white matter in these tasks, I used HARDI and CSD tractography, which permits tracking through regions of crossing fibres (Tournier et al., 2008). Using this approach, I was able to virtually dissect (Catani et al., 2002) the UF and quantify, via FA (Basser, 1997), inter-individual variation in its microstructure. Correlations were run between UF FA values and inter-individual differences on the tasks of facial emotion and identity processing, to assess the behavioural relevance of individual differences in UF microstructure. Increases in FA are typically associated with microstructural properties that support the efficient transfer of information along white matter tracts (Beaulieu, 2002). I therefore hypothesized that higher FA values in the UF, especially in the RH (Adolphs, 2002), but not FA of a control tract (the corticospinal tract, (CST)), would be associated with better facial emotion decoding ability, but not facial identity discrimination ability.

2.2 Material and Methods

2.2.1 Participants

Participants in both experiments were scanned using an identical DWI sequence. Across the two experiments, data were collected from a total of 86 participants, all of whom self-reported as being healthy and having no history of psychiatric or neurological illness. Experiment 1 comprised 42 individuals (aged 19-40 years, M=24 ± 6; 9 males) and Experiment 2 comprised a separate set of 44 individuals (aged 18-34 years, M=24 ± 4; 14 males). All participants provided written informed

consent prior to participation. The work was conducted in line with the Declaration of Helsinki and was approved by the Cardiff University School of Psychology Research Ethics Committee.

2.2.2 MRI data acquisition

Imaging data were collected at the Cardiff University Brain Research Imaging Centre (CUBRIC) using a 3T GE HDx Magnetic resonance imaging (MRI) system (General Electric Healthcare, Milwaukee, WI) with an 8-channel receive-only head RF coil. Whole brain HARDI data (Tuch et al., 2002) were acquired using a diffusion-weighted single-shot echo-planar imaging pulse sequence with the following parameters: TE=87ms; voxel dimensions=2.4 x 2.4 x 2.4 mm^3; field of view=23 x 23 cm^2; 96 x 96 acquisition matrix; 60 contiguous slices acquired along an oblique-axial plane with a slice thickness of 2.4mm and no between-slice gap. To reduce artefacts arising from pulsatile motion, acquisitions were cardiac-gated using a peripheral pulse-oximeter. Gradients were applied along 30 isotropically distributed directions with b=1200 s/mm^2. Three non-diffusion-weighted images (DWI) with b=0 s/mm^2 were also acquired according to an optimised gradient vector scheme (Jones et al., 1999). In addition, high-resolution anatomical images were acquired using a standard T1-weighted 3D FSPGR sequence comprising 178 axial slices (TR/TE = 7.8/3.0 s, FOV = 256 × 256 × 176 mm, 256 × 256 × 176 data matrix, 20° flip angle, and 1 mm isotropic resolution).

2.2.2.1 Diffusion MRI pre-processing

*ExploreDTI*_4.8.3 (Leemans, Jeurissen, & Jones, 2009) was used to correct for subject head motion and eddy current distortions. To correct for partial volume artefacts arising from voxel-wise free water contamination, the two-compartment 'free water elimination' procedure was implemented (Pasternak, Sochen, Gur, Intrator, & Assaf, 2009) yielding voxel-wise maps of free water-corrected FA.

2.2.2.2 Tractography

Tractography (Conturo et al., 1999) was performed in native diffusion space in *ExploreDTI*, using deterministic tracking based on CSD (Tournier et al., 2004), which extracts peaks in the fibre orientation density function in each voxel. The fibre orientation density function quantifies the proportion of fibres in a voxel pointing in each direction and so information about more complex

fibre configurations can be extracted (Jones et al., 2013). This approach was chosen as the most appropriate technique for reconstruction of the UF, because of its proximity to other white matter tracts (e.g. the anterior commissure) leading to crossing/kissing fibre combinations (Ebeling & von Cramon, 1992). For each voxel, streamlines were initiated along any peak in the fibre orientation that exceeded an amplitude of 0.1 (hence, multiple fibre pathways could be generated from any voxel). Each streamline continued, in 0.5mm steps, following the peak in the orientation that subtended the smallest angle to the incoming trajectory (subject to a threshold of 60˚ to prevent the reconstruction of anatomically implausible fibres). Once whole-brain tractography was complete, regions-of-interest (ROIs) were used to virtually dissect the UF and the CST. The resulting tract masks were intersected with the voxel-wise free-water corrected whole-brain FA map to obtain tract-specific free-water corrected measures of FA.

2.2.2.2.1 Uncinate Fasciculus (UF)

Three-dimensional reconstruction of the UF was performed using a multiple region of interest (ROI) approach, extracting the left and right UF separately. ROIs were manually drawn in native diffusion space on colour-coded fibre orientation maps (Pajevic & Pierpaoli, 1999), using landmark techniques previously shown to be highly reproducible (Catani & Thiebaut de Schotten, 2008; Wakana et al., 2007). A SEED ROI was drawn on a coronal slice located just anterior to the CC in the inferior medial region where the UF enters the frontal lobe (see Figure 2.1). Two AND gates were then placed in the temporal lobe, one gate encompassed the whole of the white matter of the ATL and was drawn on a coronal slice located just anterior to where the temporal lobe meets the frontal lobe. The other gate was drawn on an axial slice located in line with the upper portion of the pons, around a bundle of fibres oriented in the superior-inferior direction in the temporal white matter, capturing the region where the UF curves around the Sylvian fissure. Two NOT ROI gates were then placed to exclude fibres from other tracts. One NOT ROI was placed on a coronal slice located posterior to the pons, the gate covered the entire brain to prevent fibres from the inferior fronto-occipital fasciculus from being included. A second NOT gate was placed on a sagittal slice located between the two hemispheres. The gate covered the entire brain and was placed to ensure no fibres were included from commissural tracts such as the anterior commissure. Each tract was visually inspected to ensure the tract was consistent with the UF and did not include any erroneous fibres. Additional NOT gates were placed to remove any fibres which were inconsistent with the known path of the UF (Catani & Thiebaut de Schotten, 2008; Wakana et al., 2007).

2.2.2.2.2 Corticospinal Tract (CST)

To confirm the anatomical specificity of any effects in the UF, the above tractography protocol was additionally carried out to extract FA indices from both the LH and RH of a major motor system tract, the CST (Lemon, 2008). The CST was extracted as described previously (Wakana et al., 2007). The CST was defined as the tract running between the primary motor cortex and the mid-brain (Farquharson et al., 2013; Thiebaut de Schotten et al., 2011). An AND gate was placed in an axial slice located just superior to the superior colliculus, this gate encompassed the entire cerebral peduncle on either the left or the right side depending on the tract being extracted (see Figure 2.1). A second AND gate encompassed the anterior branch of the CST just superior to where the tract splits to run either side of the central sulcus. As with the protocol for the other tracts, NOT gates were placed to exclude fibres clearly belonging to tracts other than the CST.

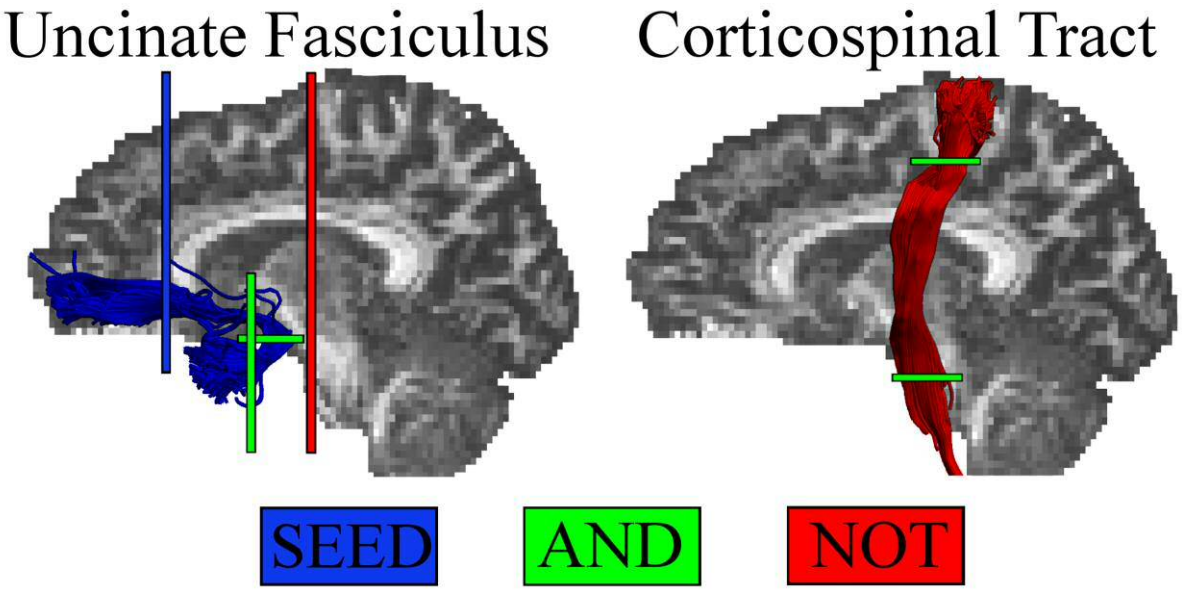

Figure 2.1. Example reconstruction of the uncinate fasciculus (UF) and corticospinal tract (CST) from a single participant. *The waypoint regions-of-interest (ROIs) used for reconstructing each tract are shown.*

2.2.3 Tasks and procedure

2.2.3.1 Experiment 1

2.2.3.1.1 Reading the Mind in the Eyes Test (RMET)

Participants completed the RMET (Baron-Cohen et al., 2001) as part of a larger testing battery. The RMET was utilised as it is a reliable and sensitive measure of subtle individual differences in face-based mental state decoding in the typical population, without being susceptible to floor or ceiling effects (Vellante et al., 2013). The RMET consists of 36 grey scale photographs, cropped to depict the eye region of a series of adult faces, each display a different complex mental state (e.g. *guilt, curiosity*). Images are surrounded at each corner by four mental state terms (1 target and 3 foils) and for each image participants are required to correctly select the word that best describes the mental state being expressed (see Figure 2.2A for a sample item).

A pen and paper version of this task was utilised and no time limit was imposed. Taken from magazine photos, images were standardised to a size of 11.5cm by 4.5cm; cropped such that each image displayed the eye region from just above the eyebrow to halfway down the bridge of the nose; and displayed on a white background (Baron Cohen et al., 2001). A glossary with definitions of the mental state terms and examples of their use was provided to reduce potential confounding with vocabulary skills. Participants scored 1 point for each correct answer, and test scores were calculated as the total number of correct responses (maximum score 36) and then converted to percentage correct values. The 36 eyes stimuli have previously been classified into three valence categories: positive (8 trials, e.g., *playful),* negative (12 trials, e.g., *upset*) and neutral, non-emotional, cognitive state trials (16 trials, e.g., *insisting*) (Harkness, Sabbagh, Jacobson, Chowdrey, & Chen, 2005). In addition to total scores, I therefore also computed total scores for cognitive and emotional items separately. Positive and negatively valenced trials were combined to form an emotional category. Scores for cognitive and emotional categories were expressed as percentage correct values.

2.2.3.1.2 Facial identity discrimination

A subset of 22 participants also completed a task of face-based identity discrimination, the odd-identity-out task (Hodgetts et al., 2015; Lee, Scahill, & Graham, 2008). In this task participants were presented with a series of face 'triads' and were instructed to select the odd-one-out as quickly and as accurately as possible. On each trial, two of the faces were the same individual presented from different viewpoints, and the target ('oddity') was a different face presented from a different viewpoint. An equal number of targets appeared at each screen position in the triad (i.e., top centre; bottom left; bottom right). Face stimuli were grey scale photographs of adult faces, half of whom were male. Individual faces were overlaid on a black background (see Figure 2.2B). Stimuli were presented using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com). Fifty-five trials were completed, each trial (1 triad) was presented for 1500ms, but no response time limit was imposed. Performance was quantified as the percentage of trials answered correctly.

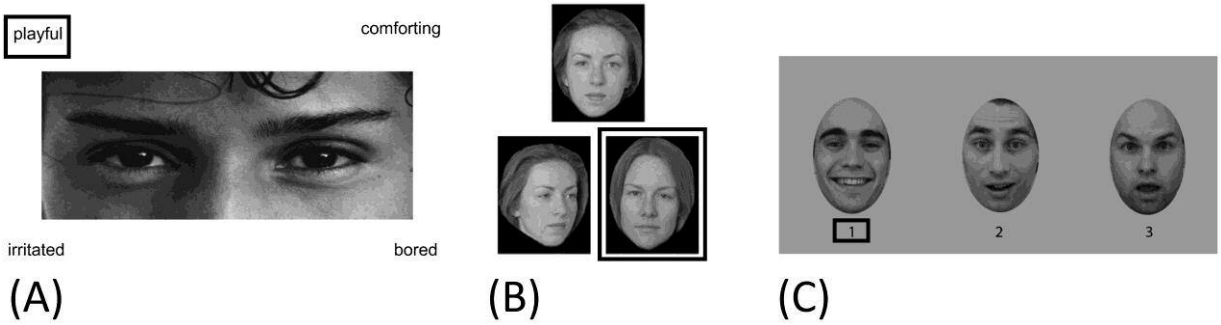

Figure 2.2. Example trials from each of the experimental tasks. (A) Reading the Mind in the Eyes Test; (B) Odd-Identity-Out Task; (C) Odd-Emotion-Out Task. For each example, the target stimulus is identified.

2.2.3.2 Experiment 2

Participants completed the tasks described here as part of a larger testing battery. In addition to the RMET and odd-identity-out tasks described above, participants in Experiment 2 additionally completed an odd-emotion-out task (Palermo et al., 2013), described below.

2.2.3.2.1 Facial Emotional Expression Discrimination

In the odd-emotion-out task (Palermo et al., 2013), a triad of faces was presented on every trial. Each face within each triad was of a different individual, each triad was matched on gender and was show from the same viewpoint (either full-face, left-facing three-quarter or right-facing three-quarter pose). Face stimuli consisted of full-colour images of individuals from the Karolinska Directed Emotional Faces database (Lundqvist, 1998). Each face was enclosed in an oval that excluded most of the hair (see Figure 2.2C for an example), and distracting facial blemishes were airbrushed out. Expressions included were the 6 so-called "basic emotions" (happiness, sadness, surprise, anger, disgust and fear) (Ekman, 1992b). Two faces within each triad showed the same emotional expression while the third showed a different emotional expression (See Figure 2.2C). Each target ('oddity') face was placed within a triad with two other faces displaying an emotion with which the target emotion is maximally confused (Young et al., 1997) (e.g. a disgust 'oddity' face paired with 2 angry foils). An equal number of target faces appeared at each screen position in the triad (i.e. left; centre; right). In order to encourage processing of facial expressions, on each trial targets and foils were matched on low level features such that, for example, open-mouthed surprise faces were paired with open-mouthed happy expressions. Participants were asked to identify the face displaying the 'odd-one-out' emotion expression.

Triads were presented for 1500ms and participants were instructed to respond as quickly and accurately as possible, but no time limit was imposed for responses. There were 100 trials in total and an accuracy score of percentage of trials correct was calculated. Stimuli were presented using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com). This task has previously been shown to be a reliable and sensitive measure of individual differences in face emotion processing in the typical adult population, without being susceptible to floor or ceiling effects (Palermo et al., 2013).

2.2.4 Statistical analysis

For both experiments, exploratory data analysis was carried out to assess the normality of the data distribution and to check for outliers, considered here to be data points beyond three standard deviations from the mean. No variables diverged substantially from normality and therefore parametric statistical analyses were conducted. Directional Pearson's correlation coefficients were calculated to determine the relationship between mean FA values for each tract and performance on the behavioural measures of interest. As I assessed both LH and RH UF, Pearson's correlations were Bonferroni-corrected by dividing $\alpha=0.05/2=0.025$. A directional Steiger z-test was used (Steiger, 1980) for the statistical test of the difference between two correlation coefficients obtained from the same sample, with the two correlations sharing one variable in common, implemented within an online calculator (Lee & Preacher, 2013).

In line with the recommendations of Dienes (2017), complementary default JZS Bayes factors were computed for each p-value (Wetzels & Wagenmakers, 2012). The Bayes factor, expressed as $BF_{10,}$ grades on a continuous scale the intensity of the evidence for the alternative hypothesis (H1) versus the null (H0). A BF_{10} of 1 indicates that the observed finding is equally likely under the null and the alternative hypothesis. A BF_{10} much greater than 1 allows us to conclude that there is substantial evidence for the alternative over the null. Conversely BF_{10} values substantially less than 1 provide strong evidence in favour of the null over the alternative hypothesis (Wetzels et al., 2011). For example, a BF_{10} of 10 indicates that the finding is 10 times more likely to have occurred under the alternative hypothesis. Analogously, a BF_{10} of 0.1 is the same as a BF_{01} of 10 (i.e. 1/0.1 = 10) and indicates that the finding is 10 times more likely to have occurred under the null hypothesis (Wetzels & Wagenmakers, 2012). Some authors have suggested discrete categories of evidential strength (such that, for example a BF_{10} between 3 and 10 indicates "substantial" evidence for H1 and a BF_{10} between 1/3 and 1/10 indicates "substantial" evidence for H0), but it is important to emphasise the arbitrary nature of these labels and the continuous nature of the Bayes factor (Wetzels & Wagenmakers, 2012).

For all tests of association, the alternative hypothesis (H1) specifies that the correlation is positive (BF_{+0}). Default Bayes Factors and 95% Bayesian credibility intervals (CIs) were calculated using JASP [version 0.8] (https://jasp-stats.org).

2.3 Results

2.3.1 Experiment 1

2.3.1.1 Behavioural performance

Participants' total scores on the RMET (M=81.2±7.9%, range 61-94%) were in line with those previously reported in similar samples (Baron-Cohen et al., 2001), as were the scores on the odd-identity-out task (M=88±S.D, range 70-96%) (Hodgetts et al., 2015). Scores on the RMET and odd-identity-out task were not significantly correlated (r=-0.007, *p*=0.975, BF_{+0}=0.258, 95% CI=-0.006, 0.444), indicating that performance on the two tasks is dependent on at least partly separable cognitive processes (Palermo et al., 2013).

2.3.1.2 Uncinate fasciculus microstructure

The UF and CST were reconstructed from both hemispheres for all participants. FA scores of the UF (M=0.420±0.0265, range=0.347–0.470) were in line with previous work (Metzler-Baddeley, Jones, Belaroussi, Aggleton, & O'Sullivan, 2011). Hemispheric asymmetry (typically right > left) in the UF has been previously observed for both volume and FA (Hau et al., 2016; Thomas, Avram, Pierpaoli, & Baker, 2015), although not all studies find such asymmetry (Thiebaut de Schotten et al., 2011). Here, a within subjects t-test revealed that right UF FA (M=0.425±0.025) was significantly greater than left UF FA (M=0.415, S.D=0.031), (t(41)=2.38, *p*=0.022, BF_{+0}=4.098, Hedges' g_{av}=0.349) (Lakens, 2013). Given this, together with the broad consensus in favour of a RH bias in emotion expression processing (Adolphs, 2002), all analyses were carried out for the left and right UF separately.

2.3.1.3 Structure-behaviour associations

2.3.1.3.1 Reading the Mind in the Eyes Test (RMET)

A significant positive correlation was found between performance on the RMET (total accuracy score) and FA in the right (r=0.421, *p*=0.003, BF_{+0}=15.93, 95% CI=0.132, 0.629*)* but not the left UF (r=0.123, *p*=0.219, BF_{+0}=0.399, 95% CI=-0.010, 0.413). The correlation between right UF FA and

RMET was significantly stronger than that between left UF FA and RMET (z=2.00, *p*=0.023), consistent with RH dominance.

To determine whether the relation observed between right UF and RMET was anatomically specific, I examined the correlation between RMET performance and FA of the CST. There was no significant correlation between RMET performance and FA in either the right (r=0.080, *p*=0.308, BF_{+0}=0.299, 95% CI=-0.007, 0.384) or left CST (r=0.049, *p*=0.110, BF_{+0}=0.248, 95% CI=-0.006, 0.364). Importantly, the correlation between RMET performance and FA of the right UF was significantly stronger than that between RMET performance and FA in the right CST (z=2.05, *p*=0.02).

2.3.1.3.2 Reading the Mind in the Eyes Test (RMET): Emotional vs. Cognitive Items

As mentioned in the methods section, RMET contains items that require the decoding of both affective and cognitive mental states, a division that has been employed in previous research. In particular, the amygdala appears critical for processing emotional, but not the cognitive (emotionally neutral) RMET items (Adolphs et al., 2002). Thus, analyses were run to further investigate whether the relationship observed between FA in the right UF was unique to emotional expressions or was common to both emotional and cognitive expressions. Performance for the cognitive items of the RMET did not show any significant relationships to FA in any of the tracts of interest including right UF (r=0.227, *p*=0.074, BF_{+0}=0.971, 95% CI=-0.022, 0.487, See Figure 2.3). In contrast, performance on the emotional items of the RMET was significantly correlated with FA in the right UF (r=0.416, *p*=0.003, BF_{+0}=14.359, 95% CI=0.126, 0.625) but not the left UF (r=0.153, *p*=0.167, BF_{+0}=0.500, 95% CI=-0.012, 0.434). While the correlation between right UF FA and RMET was greater for emotional vs. cognitive items, this difference failed to reach statistical significance (z=1.02, *p*=0.154). As seen with total RMET performance, however, the correlation for emotional RMET items alone was stronger with right UF than with left UF (z=1.765, *p*=0.039), implying that microstructure of the right, but not the left UF, is preferentially linked to facial emotion expression decoding ability.

As mentioned in the introduction to this chapter, it has been suggested that the RH might play a disproportionate role in processing only emotions with a negative valence (e.g. Adolphs et al., (2001); Reuter-Lorenz, Givis, & Moscovitch, (1983)). When looking at the positive and negative valence RMET separately, a significant association was observed between positive items and right

UF FA (r=0.422, *p*=0.005, BF_{+0}= 16.17, 95% CI = 0.132, 0.630). A positive correlation between negative RMET items and right UF FA was also seen, but this failed to reach statistical significance (r=0.263, p=0.093, BF_{+0}=1.432, 95% CI = 0.030, 0513). The correlation between right UF FA and positive valence RMET items was not however, significantly stronger than that for negatively valenced items (Z=-0.846, *p*=0.199). The correlation between cognitive items and right UF FA was not seen to be significantly different from the correlations between negative items (z=0.186, *p*=0.426) or positive items (z=0.986, *p*=0.162) and right UF FA.

2.3.1.3.3 Facial identity discrimination

To determine whether observed associations might reflect a broader role for the UF in processing facial expression *and* facial identity, I examined the correlation between UF FA and performance on the odd-identity-out task. In contrast to the RMET, no significant correlations were observed between odd-identity-out task performance and FA in any of the tracts of interest (right UF: r=0.118, *p*=0.301, BF_{+0}=0.415, 95% CI=-0.010, 0.511; left UF: r=0.377, *p*=0.042, BF_{+0}=2.048, 95% CI=-0.042, 0.664; right CST: r=0.197, *p*=0.190, BF_{+0}=0.607, 95% CI=-0.014, 0.557; left CST: r=0.272, *p*=0.110, BF_{+0}=0.943, 95% CI=-0.022, 0.601). In this smaller subset of participants (n = 22/42), a significant correlation was observed between FA in the right UF and total RMET performance (r=0.478, *p*=0.025, BF_{+0}=5.596, 95% CI= 0.091, 0.725), however the correlation between right UF FA and RMET was not significantly stronger than that between right UF FA and odd-identity-out performance (z=1.217, p=0.111), likely due to lack of statistical power.

2.3.1.4 Summary- Experiment 1

Microstructure (FA) of the right, but not left, UF was significantly associated with performance on the RMET, especially for emotional, relative to non-emotional, items, but was not significantly associated with performance on the odd-identity-out task. This suggests that the right UF may play an important role in the decoding of emotional content in facial expression, but be less critical to facial identity discrimination. To bolster these findings, in Experiment 2 I aimed firstly to replicate, in an independent sample, the association between right UF microstructure and performance on the emotional items of the RMET, and the non-association with odd-identity-out performance. Secondly I aimed to overcome one potentially confounding aspect of the previous experiment, the presence of an explicit labelling requirement in the RMET that was not present in the odd-identity-

out task. To account for this procedural difference, Experiment 2 included a facial odd-emotion-out discrimination task, analogous to the odd-identity-out task used in Experiment 1. This allowed us to determine whether the correlation seen between facial emotion decoding and FA within the right UF still remained when there was no overt requirement for participants to name the emotion expressed in the face.

2.3.2 Experiment 2

2.3.2.1 Behavioural performance

Odd-identity-out performance for one individual was clearly an outlier, sitting almost 5 standard deviations below the mean and over 3 standard deviations below the nearest data point. This data point was removed prior to analysis of data for Experiment 2. As in Experiment 1, all variables of interest were normally distributed and thus parametric analyses with Pearson's r were conducted.

While performance on the RMET was slightly lower in Experiment 2 than in Experiment 1, and scores showed greater variability (M=79.9±9.7%, range 56-97%), performance did not significantly differ between Experiment 1 and 2 ($t(84)=0.671$, $p=0.504$, $BF_{10}=0.274$). Participant performance on the odd-identity-out task was also very similar across experiments (M=89.0±6.7%, range 70-100%), and did not significantly differ ($t(63)=-0.687$, $p=0.495$, $BF_{10}=0.324$). Performance on the odd-emotion-out task (M=72.9±6.4%) was in line with that reported in previous work (Palermo et al., 2013).

A significant positive correlation was observed between total performance on RMET and the odd-emotion-out task ($r=0.457$, $p=0.001$, $BF_{+0}=30.40$, 95% CI=0.166, 0.657), indicating that these two tasks involve highly similar cognitive processes and suggesting that performance on the RMET is strongly linked to facial emotion discrimination abilities. This correlation was additionally observed between the emotional items of the RMET and odd-emotion-out performance ($r=0.357$, $p=0.022$, $BF_{+0}=4.817$, 95% CI=0.073, 0.585).

In line with Experiment 1, no significant correlation was observed between total RMET performance and scores on the odd-identity-out task ($r=0.162$, $p=0.150$, $BF_{+0}=0.539$, 95% CI=-0.013, 0.437) or between the emotional items of the RMET and odd-identity-out task ($r=0.162$,

p=0.298, BF_{+0}=0.543, 95% CI=-0.013, 0.438). In contrast, a significant correlation was found between performance on the odd-identity-out task and that on the odd-emotion-out task (r=0.460, *p*=0.001, BF_{+0}=29.296, 95% CI=0.166, 0.661), suggesting that these tasks require some shared perceptual mechanisms of face processing (Palermo et al., 2013). These patterns of dissociation and association are similar to those seen in previous work (Palermo et al., 2013).

2.3.2.2 Uncinate fasciculus microstructure

UF FA values were highly similar to those obtained in Experiment 1 (M=0.418±0.0315, range=0.331–0.499). FA values were not significantly different from those seen in Experiment 1 for either right UF (t(84)=0.716, *p*=0.476, BF_{10}=0.282) or left UF (t(83)=-0.211, *p*=0.833, BF_{10}=0.231). A within subjects t-test was again run comparing FA in the right versus left UF. Unlike in Experiment 1, while right UF values were numerically greater than left, no significant difference was seen between FA in the right (M=0.421, S.D=0.029) and left (M=0.416±0.0344) UF in this sample (t(42)=1.00, *p*=0.321, BF_{+0}=0.440, Hedges' g_{av}=0.157). Analyses were nevertheless, run for each hemisphere separately due to strong predictions about RH dominance for facial expression decoding.

2.3.2.3 Structure-behaviour associations

2.3.2.3.1 Reading the Mind in the Eyes Test (RMET)

Consistent with Experiment 1, a significant association was observed between FA in the right UF and scores on the emotional items of the RMET (r=0.371, *p*=0.007, BF_{+0}=7.246, 95% CI=0.091, 0.588, see Figure 2.3), further supporting the claim that emotional items within the RMET underlie the relationship with right UF microstructure. Furthermore, no significant association was observed between FA in the right UF and performance on the cognitive items within the RMET (r=-0.132, *p*=0.394, BF_{+0}=0.108, 95% CI=-0.003, 0.254). These two correlations were seen to be significantly different from one another (z=-2.774, *p*=0.003). In line with Experiment 1, there was no significant relationship between FA in the left UF and RMET total score (r=-0.078, *p*=0.310, BF_{+0}=0.134, 95% CI=-0.003, 0.286) or performance on emotional RMET items (r=0.082, *p*=0.600, BF_{+0}=0.302, 95% CI =-0.007, 0.382). Indeed, a significant difference was seen in the correlation between RMET performance and FA in the right as compared to FA left UF for both RMET total

score (z=1.878, *p*=0.030), and the emotional sub-scale score (z=2.06, *p*=0.020), consistent with a right lateralisation of this association.

In contrast to Experiment 1, when separating emotional RMET trials by valence, a significant association was observed between negative items and right UF FA (r=0.410, p=0.003, BF_{+0}=14.96, 95% CI = 0.127, 0.617), but the correlation between positive items and right UF FA failed to reach statistical significance (r=0.161, p=0.149, BF_{+0}=0.538, 95% CI = 0.013, 0.433). The difference between these correlations just failed to reach significance (Z=1.463, *p*=0.072). As in Experiment 1, no statistically significant relationship was observed between right UF FA and performance on the cognitive RMET items (r=-0.132, *p*=0.803, BF_{10}=0.267, 95% CI = -0.400, 0.167). The correlation between negative items and right UF FA was stronger than with cognitive items (z=2.58, *p*=0.005) as was the correlation between positive vs. cognitive items and right UF FA (z=1.91, *p*=0.028).

In line with the findings of Experiment 1, no significant association was observed between scores on the emotional items of the RMET and FA in either right (r= 0.053, *p*=0.367, BF_{+0}=0.250, 95% CI=-0.2480, 0.344) or left CST (r=0.025 *p*=0.435, BF_{+0}=0.215, 95% CI=-0.274, 0.320). As in Experiment 1, the correlation between performance on the emotional items of the RMET and FA of the right UF was significantly stronger than that between emotional RMET performance and FA of the right CST (z=1.726, *p*=0.04).

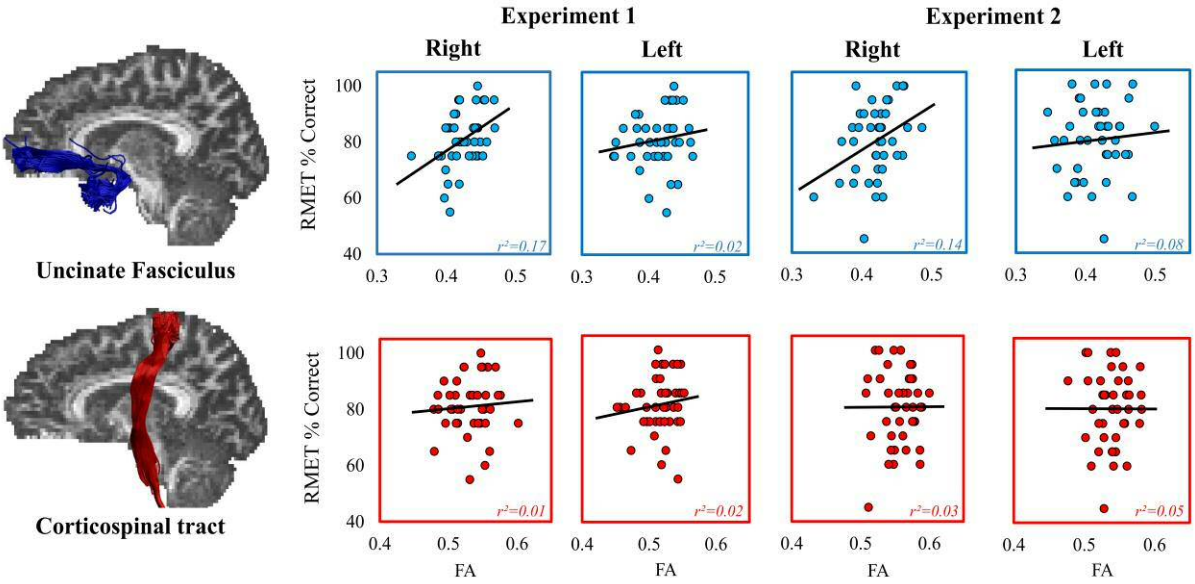

Figure 2.3. The association between fractional anisotropy (FA) in the uncinate fasciculi and corticospinal tracts and performance on the emotional trials within the Reading the Mind in the Eyes Task (RMET) for both Experiment 1 and Experiment 2. Best fitting linear regression lines are displayed on each scatter plot.

2.3.2.3.2 Emotion odd-one-out discrimination

Consistent with the hypothesis that the emotion decoding requirements of the RMET drive its association with right UF microstructure, a significant correlation was observed between odd-emotion-out discrimination performance and FA in the right (r=0.413, p=0.004, BF+0= 6.277, 95% CI=0.120, 0.639) but not left UF (r=0.054, p=0.371, BF+0=0.207, 95% CI=-0.262, 0.359, see Figure 2.4). Furthermore, these correlations significantly differed from one another (z=2.407, p=0.008). Supporting the anatomical specificity of these effects no significant relationships were seen between performance on the odd-emotion-out task and FA in either the left (r=-0.043, p= 0.395, BF+0=0.201, 95% CI=-0.346, 0.268) or the right CST (r=-0.055, p=0.367, BF+0=0.206, 95% CI=-0.356, 0.257). Indeed, a comparison of the correlations between FA in the right UF and CST showed that the correlation between emotion oddity performance and FA in the right UF was significantly stronger than the correlation with the right CST (z=2.472, p=0.007).

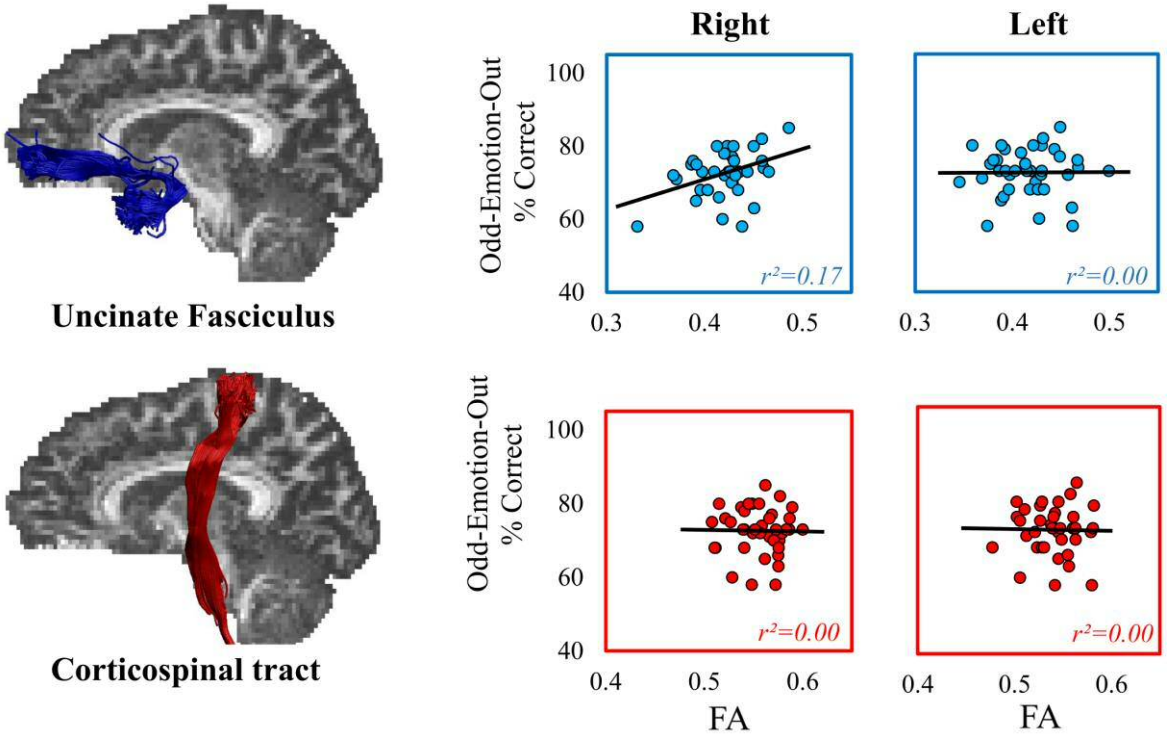

Figure 2.4. The association between Fractional Anisotropy (FA) in the uncinate fasciculi and corticospinal tracts and performance on the Odd-Emotion-Out task. Best fitting linear regression lines are displayed on each scatter plot.

2.3.2.3.3 Face identity discrimination

As in Experiment 1, there was no significant correlation between performance on the odd-identity-out task and FA in either right (r=0.079, p=0.307, BF_{+0}=0.215, 95% CI=-0.227, 0.371) or left UF (r=-0.181, p=0.126, BF_{+0}=0.362, 95% CI=-0.459, 0.130). To determine whether this absence of significant relationship between right UF and odd-identity-out performance was indeed meaningfully different from the significant relationships seen with the emotion-based tasks, comparisons were run between this correlation and the correlations previously reported between right UF and each of the other cognitive tasks. The relationship between odd-identity-out task and FA in the right UF was indeed seen to be significantly different from the correlation between right UF FA and performance on the odd-emotion-out task (z=2.193, *p*=0.014), and approached significance for the correlation with emotion items in the RMET (z=1.522, *p*=0.064). Thus, findings from this larger sample support the hypothesis that the association seen with the right UF was specific to facial *emotion* processing.

2.3.2.3.4 Bayes Multiple Regression

Finally, to examine whether performance on emotion labelling in the RMET and emotion discrimination performance from the odd-expression-out task were independently related to microstructure of the right UF, I performed Bayesian multiple regression and model comparison using JASP (Rouder & Morey, 2012).

Bayesian regression indicated that the best fitting model was one that took into account both RMET emotional labelling *and* odd-expression-out performance as predictors (BF vs. null model=8.367). The next best model contained odd-expression-out discrimination only (BF vs. null model=6.309). A model just containing RMET emotion labelling performance was also supported (BF vs. null model=4.532). These findings provide strong evidence that the relation between right UF microstructure and emotion decoding is not restricted to tasks requiring overt emotion labelling as required in the RMET.

2.4 Discussion

Facial emotion processing is a function in that may require rapid information transfer across a spatially distributed neurocognitive network. Here I focused on facial emotion processing as in bvFTD impairments are seen in the discrimination of facial expressions of emotion (Bertoux et al., 2014; Oliver et al., 2014; Rosen et al., 2002). As highlighted in the introduction to this thesis, prominent alteration is seen in bvFTD in the UF (Mahoney et al., 2014; Matsuo et al., 2008; Zhang et al., 2013) and due to its connectivity, the UF is a candidate for a white matter tract that supports facial emotion processing. Few studies have however directly considered whether UF microstructure may be related to facial emotion expression discrimination. This chapter addressed this question, informed by evidence from bvFTD and work on the functional role of grey matter regions between which the UF provides connectivity.

Across two experiments, I established the presence of a robust correlation between facial emotion processing abilities and the microstructural organisation of the right UF, but not of the left UF, or of a control tract implicated in complex motor skills (the CST) (Engel et al., 2014). In Experiment 1, I found a positive correlation between right UF FA and performance on the well-known 'Reading the Mind in the Eyes Test' (RMET), which was driven predominantly by the emotional items within the task. Experiment 2 corroborated and expanded this finding, replicating the positive correlation between right UF microstructure and performance on the emotional items of the RMET, and additionally revealing a positive correlation between right UF FA and odd-expression-out performance. Across both experiments, I found little evidence of a relationship between UF microstructure and performance on an odd-identity-out face discrimination task. My findings thus indicate that the observed relationship between right UF microstructure and emotion-based tasks reflect the emotion processing components of the tasks and not more general face-processing abilities. Taken together, my findings highlight the important role of RH frontotemporal connectivity, supported by the UF, in underpinning facial emotion processing. The results further suggest that UF alteration could have a role in facial emotion discrimination difficulties in bvFTD. The results of this work extend the existing literature by showing that, consistent with distributed network models of facial expression processing (Adolphs, 2002), the microstructural properties of UF are related to facial emotion processing.

The functional role of regions between which the UF provides connectivity makes it a strong candidate for supporting the neurocognitive network underlying facial emotion processing. In humans and non-human primates, the UF creates a direct structural connection between portions of the ATL and sectors of the OMPFC (Schmahmann et al., 2007; Thiebaut de Schotten et al., 2012). In monkeys these regions sit within the 'face patch' network - a set of interconnected regions that show stronger fMRI activation to faces than to other classes of object (Tsao et al. (2008). Convergent results are seen in human functional imaging studies, which have shown the involvement of frontal and temporal regions in both facial emotion labelling and perceptual facial emotion discrimination tasks. This includes studies of analogues of the RMET (Adams et al., 2010; Wicker et al., 2003) and facial emotion matching to sample tasks (LoPresti et al., 2008). Though the precise anatomical connectivity between frontal and temporal face patches are unclear (Grimaldi, Saleem, & Tsao, 2016), the UF, whose anatomy is highly conserved between humans and monkeys (Thiebaut de Schotten et al., 2012), is well placed to mediate the interconnection of these regions, either directly or indirectly.

UF may support facial emotion processing by enabling intercommunication within the distributed facial affect-processing network (Adolphs, 2002). This is consistent with the notion of an extended ventral visual processing stream which runs into ventrolateral prefrontal cortex (Kravitz, Saleem, Baker, Ungerleider, & Mishkin, 2013), and in which cascaded, interactive, feed forward and feedback processing mediates the discrimination of facial expression (Murray, 2017). As the anterior point of the ventral visual perceptual or 'what' stream, the ATL is a key component of a vital network for the processing and encoding of facial information (Kriegeskorte, Formisano, Sorger, & Goebel, 2007; Simmons, Reddish, Bellgowan, & Martin, 2010). Further to this, by virtue of its unique connectivity, the ATL functions to bind information from modality-specific systems to form and store coherent, transmodal, generalisable concepts, including social and emotional concepts (Binney et al., 2016; Lambon-Ralph, Jefferies, Patterson, & Rogers, 2017; Pobric, Lambon Ralph, & Zahn, 2016). The ATL thus has a key role in facial emotion comprehension (Kumfor et al., 2015).

While the ventral visual processing stream may facilitate facial perception, its interaction with the OMPFC in particular may be critical for facial emotion decoding. In monkeys, frontal face patch activity is modulated by facial expression more prominently than ATL face patches (Tsao et al. (2008). Indeed selective OMPFC damage has been seen to impair facial emotion recognition (Willis

et al., 2014), suggesting a key role for this region. Indeed damage to frontotemporal regions, especially in the RH, have shown their critical role in facial emotion processing across a variety of tasks (Kumfor, Irish, Hodges, & Piguet, 2013; Rosen et al., 2002; Rosen et al., 2006; Willis et al., 2014). The UF may thus facilitate facial emotion decoding by enabling the bidirectional flow of information between frontal and temporal lobes. The results of this chapter presents the question of what the functional contribution may be to facial emotion decoding of connectivity of the ventral visual processing steam with the frontal lobes.

One potential explanation for the importance of frontotemporal connectivity for facial emotion processing is that the connectivity provided by the UF may facilitate the integration of semantic and perceptual information regarding facial configuration with affect and reward contingencies necessary for emotion decoding. Affect judgements may require reward based input as emotion, particularly 'basic' emotions, may be underpinned by value based categorisation (Lindquist, Gendron, Barrett, & Dickerson, 2014) as reward or punishment contingencies may be very different for even highly similar facial expressions. Highly similar smiles may variously communicate relaxation, concern, or even contempt, each with very different rewarding or punishing contingencies. The reinforcement value of such facial expressions may thus be crucial for social emotional understanding, behaviour and key components of expression comprehension. Input from the OMPFC may therefore be crucial as it suppors the learning and processing of reward and punishment contingencies (Grabenhorst & Rolls, 2011; Rolls, 2004) as it represents the value of stimuli across a range of domains (Grabenhorst & Rolls, 2011), including emotions (Hynes, Baird, & Grafton, 2006) and faces (Goodkind et al., 2012). The feed forward and feedback connectivity between ATL and OMPFC, facilitated by the UF, may thus be necessary for the decoding of facial expression (Murray, 2017) by enabling emotion concept knowledge and value to support the discrimination of discrete emotion categories (Lindquist et al., 2014). This is consistent with the proposal that the UF has a critical role in facilitating stimulus representations more broadly to be associated with reward or punishment contingencies (Alm, Rolheiser, Mohamed, & Olson, 2015; Von Der Heide et al., 2013).

Whilst my findings provide strong evidence that right UF microstructure was related to facial emotion processing, I found little evidence that UF microstructure was related to facial identity processing. No significant correlation was observed between right UF FA and odd-identity-out performance. This converges with work which has shown a separation of facial emotion and

identity processing in healthy adults (Alm, Rolheiser, & Olson, 2016) and individuals with acquired brain damage (Hornak et al., 2003; Hornak et al., 1996). Consistent with the UF not having a critical role in identity processing, while ATL lesions can lead to facial identity processing impairment (Kumfor et al., 2015; Olson, Ezzyat, Plotzker, & Chatterjee, 2015), OMPFC lesions do not (Hornak et al., 1996; Willis et al., 2014). Identity processing in FTD has been reported by some to be intact (Couto et al., 2013; Keane et al., 2002; Rosen et al., 2002; Van den Stock et al., 2015), though findings are mixed (De Winter et al., 2016; Hutchings, Palermo, Piguet, & Kumfor, 2017; Kamminga, O'Callaghan, Hodges, & Irish, 2014). Given that the identities presented in this experiment were unfamiliar to the participants and therefore of little meaning or value, the absence of a relationship with the UF would be consistent with an explanation of the UF supporting the computation of reward or value.

From the current findings, it is unclear whether the observed effects are specific to facial emotion or whether they would hold for other modalities of emotion expression. If the proposal of a role for the UF in an extended affect or salience processing system were correct then this would predict that the observed association would hold for affect processing more broadly. In support of such a role in broader emotion-general processing, OMPFC and ATL damage have been seen to result in impairments in the perception of emotion from modalities other than faces, including from vocal and bodily expressions (Adolphs et al., 2001; Hornak et al., 2003; Keane et al., 2002). Indeed in bvFTD deficits in emotion perception are not only seen in facial expression but also in musical (Downey et al., 2013), bodily (Van den Stock et al., 2015), vocal (Gregory et al., 2002; Keane et al., 2002; Shany-Ur et al., 2012) and artistic expressions of emotion (Cohen et al., 2016). This suggests that the UF may be involved in broader, trans-modal aspects of emotion processing. Future studies should consider investigating the generalisability of the current findings to additional emotion expression modalities to verify this presumption.

The proposed role of the UF in contingency and reward processing would further suggests that the right frontotemporal network underpinned by the UF might be specialised for processing salient and behaviourally significant stimuli, rather than emotion expressions *per se* (Ranganath & Ritchey, 2012). According to one particularly pertinent model of the development of social skills (Chakrabarti & Baron-Cohen, 2006), a very early developing, and presumably partly innately specified (Ekman, 1992b) neural “emotion detector” is critical for the development of social attention mechanisms, including reciprocal joint attention. Consistent with a broader role for UF in

social functioning, joint attention at 9 months of age is related to microstructural properties of the right UF (Elison et al., 2013). Over development, joint attention may influence the ability to empathise with other individuals, consistent with a reduction in self-report empathy being seen following lesions to the right UF (Oishi et al., 2015). Consistent with a wider role of this network, the OMPFC has been shown to have a role in the deciphering socioemotional information, enabling socially appropriate behaviour (Goodkind et al., 2012; Kringelbach & Rolls, 2003) and to have a role in affective empathising more broadly (Shamay-Tsoory, Harari, Aharon-Peretz, & Levkovitz, 2010). OMPFC lesions additionally impact the ability to make inferences about the emotional state of others (Hynes et al., 2006; Shamay-Tsoory, 2011). Collectively, these findings provide one possible account as to why both early and late developing traits and disorders including ASD (Ameis & Catani, 2015); Psychopathy (Sobhani, Baker, Martins, Tuvblad, & Aziz-Zadeh, 2015) and FTD (Mahoney et al., 2014), which feature altered right UF microstructure, are all associated with alterations in both emotion recognition *and* empathy. It is thus feasible that the UF may have a role in supporting a broad social neurocognitive network necessary for social value processing. Again, further work is necessary to further explore this possibility.

Here, facial emotion but not cognitive state expressions were related to UF microstructure. Reports of impairment in individuals with selective amygdala lesions strikingly mirror my findings of a distinction between cognitive and emotional RMET items. Such a dissociation has been shown in individuals with bilateral and unilateral RH amygdala lesions (Adolphs, 2002; Adolphs et al., 2002; Shaw et al., 2005). Individuals with RH but not LH OMPFC lesions were seen to have specific impairment on negative valence RMET items but intact performance on cognitive items (Shaw et al., 2005). Consistent with suggestions that RH frontotemporal connectivity is particularly important for the decoding of emotional relative to cognitive mental states from faces (Sabbagh, 2004; Sakaki, Niki, & Mather, 2012; Shamay-Tsoory et al., 2009). One suggestion for why UF microstructure may be related to only emotional trials within the RMET is that non-emotional RMET items (e.g. 'insisting') may be solved by judging gaze direction alone, without requiring fine grained judgments of facial expression (Stone, Baron-Cohen, Calder, Keane, & Young, 2003). A methodological proposal that requires further investigation. A second possibility is that, consistent with the posited role of the UF, cognitive states may be far less strongly associated with reward or punishment than emotional states and thus may not carry the specific valence information intrinsic to emotional expressions.

The observation of a selective association between UF microstructure and emotional but not cognitive RMET trials is consistent with the proposed dissociable cognitive and emotional components of mentalising (Abu-Akel & Shamay-Tsoory, 2011), discussed in the introduction chapter. Consistent with the model proposed by Abu-Akel & Shamay-Tsoory (2011) OMPFC-ATL connectivity may be key for affective but not cognitive mentalising. This proposal would link well with the fact that although argued to be best viewed as a sensitive indicator of individual differences in facial emotion recognition (Oakley, Brewer, Bird, & Catmur, 2016).

The results of this work show a prominent right lateralisation of the relationship between UF microstructure and facial emotion decoding. Though there is some conflict within the literature on the hemispheric specialisation of facial emotion decoding, consistent evidence shows impairments in emotion decoding following damage to the RH (Goodkind et al., 2012; Philippi, Mehta, Grabowski, Adolphs, & Rudrauf, 2009; Rosen et al., 2002). While evidence regarding the LH is variable (Harvey, Wei, Ellmore, Hamilton, & Schnur, 2013; Pobric et al., 2016), the observed lateralisation of findings fit with the strong RH lateralisation of frontal face patch activity seen in nonhuman primates (Tsao et al., 2008). The nature and origins of RH dominance in facial emotion processing, and facial processing in general, are still largely unclear (Adolphs, 2002; Behrmann & Plaut, 2013). Neuroanatomically, my findings suggest that hemispheric asymmetry in UF microstructure may have a role in functional lateralisation. Consistent with my findings, the anterior semantic hub model proposes that while the ATL in both hemispheres supports social and emotional functioning, regions within the right TP contribute more to social and emotional concepts than their LH counterparts (Binney, Parker, & Lambon Ralph, 2012; Lambon-Ralph et al., 2017). This is suggested to occur due to increased RH TP connectivity to networks that support social perception and valence coding, with the left more strongly connected to LH language centres. Consistent with DWI tractography studies indeed suggest greater RH connectivity (indexed by number of streamlines) between OMPFC and TP cortex, mediated by UF fibres (Binney et al., 2012; Hau et al., 2016; Papinutto et al., 2016).

One much debated issue concerns the extent to which the RH might play a disproportionate role in processing all emotions or only emotions with a negative valence. Some have suggested that positive emotion processing may rely on the LH (Reuter-Lorenz et al., 1983), or bilateral processing (Adolphs et al., 2001). Uncertainty may be pre sent partly due to methodological differences in experiments. Studies in this area vary by lesion type, severity, and chronicity in neuropsychological

studies, as well as variations in the tasks and stimuli used to assess facial emotion decoding. Typically, studies are imbalanced in terms of the number of positive and negative expressions tested (i.e. one positive – happy - versus several negative). My findings can speak to this question to some extent as the RMET, which contains several different positive and negative expressions, are not consistent with a valence hypothesis, but clearly indicate that the RH is disproportionately important in the processing of face emotion. It does however remain a fundamental question why emotion processing should feature hemispheric lateralisation.

Biological interpretations of individual differences in FA are challenging to make as differences in FA may vary due to a plethora of functionally relevant biological properties of white matter such as myelination, membrane permeability, axonal number, diameter and configuration (Jones, Knösche, et al., 2013). Each of these properties may differently impact on the transmission of information between neural regions. Such underlying microstructural properties are important for facilitating information transmission between distributed neural regions. For instance, activity-dependent variation in axon myelination may support synchronised functional coupling between distal brain regions by regulating conduction velocities (Fields, 2008). One study has however found strong correspondence between myelin microstructure and DTI microstructural indices, where high FA was linked to high myelin density (Seehaus et al., 2015).

While the causes of inter-individual variation in white matter microstructure are not fully understood, they likely include a complex interplay between genetic and environmental factors over the life course. The microstructure of the UF has been shown to be highly heritable (Budisavljevic et al., 2016), and in a recent study, microstructure of the right UF measured at just 6 months of age predicted infants' reciprocal joint attention skills at 9 months of age (Elison et al., 2013). At the same time, the UF is a relatively late maturing tract, showing microstructural alteration into the fourth decade of life (Lebel et al., 2012) (notably in synchrony with the late maturation of facial emotion recognition abilities, Hartshorne and Germine (2015)), suggesting that its development can also be shaped by experience. Thus, UF microstructure is likely to both shape, and be shaped by, social interaction in a transactional fashion (Gottlieb, 1991).

In summary, across two experiments, I showed in this chapter that individual differences in the microstructure of the right UF, a structure whose function has remained rather enigmatic (Von Der Heide et al. (2013), predicted individual differences in two distinct tasks of facial emotion

processing, but was not related to individual differences in facial identity processing. This result is consistent with a role for an extended right frontotemporal network, interconnected via the UF, in the decoding of this important class of social stimuli. This effect may be a result of a broader role in the encoding and reconstruction of the emotional value, salience and meaning of stimuli, though further work is necessary to validate this proposal. This work may have important implications for our understanding of the impact of UF alteration in conditions such as FTD and ASD. It further highlights the value of investigating in healthy adults the relationship between functions and white matter structures that show alteration in bvFTD, by showing how such an investigation can provide converging evidence for proposals of the underlying causes of functional alterations.

3

The Cingulum Bundle: Backbone of the Social Brain?

3.1 Introduction

The cingulum bundle (CB) is one of the brain's major white matter pathways. It is found beneath the cingulate cortices wrapped around the CC at the medial edges of the cerebral hemispheres, (Catani & Thiebaut de Schotten, 2008). The CB principally connects medial aspects of the ACC and PCC with medial frontal, parietal and temporal brain regions (Schmahmann et al., 2007). Its longest fibres, however, run from the parahippocampal gyrus through to subgenual portions of the frontal lobe (Catani et al., 2002; Heilbronner & Haber, 2014; Schmahmann et al., 2007).

Though limited research has investigated the functional role of the CB, its location and connectivity suggest that it may have an important role in supporting cognitive empathy. The CB has been described as one of the brain's main limbic pathways (Catani et al., 2013), and the anterior CB in particular provides structural connectivity between key regions which sit within posited social cognitive networks, such as the precuneus and dorsomedial PFC (Catani et al., 2013; Catani & Thiebaut de Schotten, 2008)(See introduction chapter, Figures 1.1 and 1.2). It seems feasible that the CB may have a role in supporting cognitive empathy as social cognitive tasks lead to increased activity in the cortical regions that are interconnected by the CB, such as the ACC, vmPFC, precuneus and PCC (Hyatt, Calhoun, Pearlson, & Assaf, 2015; Mars et al., 2012; Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008; Sebastian et al., 2011). Mentalising, which underlies cognitive empathy (Blair 2005; Zaki & Ochsner, 2009), is in particular associated with a network of consistently co-activated regions in the medial frontal, temporal and parietal lobes, including the TPJ, superior temporal sulcus, medial PFC (mPFC) and the precuneus (Frith & Frith, 2003; Saxe & Kanwisher, 2003)(See introduction, Figure 1.2). These regions show, in particular, task-related co-activity during tasks involving inferences about the intentions of others (Dufour et al., 2013; Spunt & Adolphs, 2014; Yoshida, Seymour, Friston, & Dolan, 2010). As the CB may provide connectivity between several of these regions, it is likely that its structural properties will

affect their ability to intercommunicate, and therefore the microstructural properties of the CB may be related to mentalising abilities. Indeed, the microstructural properties of the CB are related to the functional connectivity of regions such as the PCC and mPFC (van den Heuvel et al., 2008), whose functional connectivity can be modulated by social cognitive tasks (Li, Mai, & Liu, 2014).

Existing evidence from the ASD literature provides some support for the suggestion that the CB may have a role in supporting mentalising. Individuals with ASD, a developmental condition characterised by impaired mentalising, have been shown to have abnormal functional connectivity between regions connected by the CB, both during rest (Anderson et al., 2011; Weng et al., 2010) and during a social cognitive task (Murdaugh, Nadendla, & Kana, 2014). Indeed, in high-functioning individuals with ASD, functional connectivity between the mPFC and precuneus, regions connected by the CB, have been seen to be associated with levels of social responsiveness (Assaf et al., 2010). Though these studies did not consider the role of the CB in mediating this connectivity, alteration of the CB has been argued to be present in ASD (Ameis & Catani, 2015) and an absence of typical developmental changes in the CB have been observed in individuals with ASD (Ikuta et al., 2014). Though resection of the left CB has been seen to be a strong predictor of impaired social cognition (Herbet et al., 2015), few studies have directly investigated the relationship between the microstructural properties of the CB and mentalising in healthy adults.

Though often treated as a single structure, work using axonal tracing and diffusion tractography has shown the CB to be comprised of multiple, anatomically separable pathways (Heilbronner & Haber, 2014; Jones, Christiansen, et al., 2013). Using tractography (as described in Chapter 1) the CB has been sub-divided into three separable pathways: The parahippocampal, retrosplenial and subgenual CB (Jones, Christiansen, et al., 2013)(see figure 3.1). The subgenual CB is proposed to primarily originate around the ACC, with fibres extending from the vmPFC, and amygdala. These fibres project to the PCC and anterior thalamic nuclei (Heilbronner & Haber, 2014; Jones, Christiansen, et al., 2013). Retrosplenial fibres do not extend as far round the anterior end of the CC as those of the subgenual CB, and project to the dorsal prefrontal cortex, while parahippocampal fibres project to the medial temporal lobe (Heilbronner & Haber, 2014; Jones, Christiansen, et al., 2013). These pathways have been seen to differ in their microstructural properties (Jones, Christiansen, et al., 2013), suggesting both that they may be subject to different developmental and biological pressures and that they may underpin different functions. This

variability means that it is important to split the CB into these constituent components when considering the structure-to-function relationships of this region of white matter, as it suggests that each may support different cognitive functions.

Anterior portions of the CB, and thus principally the subgenual cingulum, seem particularly likely to have a role in mentalising. As highlighted in the Chapter 1, alterations in the CB are often seen in bvFTD (Mahoney et al., 2014; Whitwell et al., 2010; Zhang et al., 2011; Zhang et al., 2009) and may be one of the earliest structural changes in FTD, being seen in even in pre-symptomatic individuals at high genetic risk for FTD (Dopper et al., 2013; Pievani et al., 2014). CB alteration has been described as a hallmark feature of bvFTD (Lillo, Mioshi, Burrell, et al., 2012) and has been seen to be valuable for the discrimination of those with bvFTD from healthy adults (Agosta, Scola, et al., 2012; Mahoney et al., 2014; Santillo, Mårtensson, et al., 2013). Anterior portions in particular appear sensitive to the presence of bvFTD (Zhang et al., 2009), consistent with the observation that in bvFTD there is prominent grey matter atrophy in the adjacent ACC (Borroni et al., 2007; Lillo, Mioshi, Burrell, et al., 2012; Rohrer et al., 2010; Zhang et al., 2011; Zhang et al., 2013). Given that mentalising is impaired early on in bvFTD on a broad array of assessments (Bejanin et al., 2017; Bora et al., 2015; Fernandez-Duque et al., 2010; Gregory et al., 2002; Henry et al., 2014; Lough et al., 2001; Lough & Hodges, 2002; Torralva et al., 2007) it seems feasible that anterior portions of the CB may have a critical role in supporting mentalising, and underlying early bvFTD symptoms. In line with this, it is only in anterior sections of the CB that associations have been observed with social cognition in psychopathy (Sethi et al., 2015) or with disease status in disorders involving social cognition (Santillo, Mårtensson, et al., 2013; Zhang et al., 2009). In some work, in bvFTD, limited or no changes have been reported in the posterior divisions of the CB (Zhang et al., 2009).

A challenge for investigating mentalising in healthy adults is that most tasks show limited inter-individual variability (Dodell-Feder, DeLisi, & Hooker, 2014; Duval et al., 2012; Freedman et al., 2013; Gregory et al., 2002; Lough & Hodges, 2002; Torralva et al., 2007; Torralva et al., 2009). This impedes the investigation of individual differences in mentalising, despite clear variability in the healthy adult population. It may be unsurprising that most adults show ceiling levels of performance on most mentalising tasks when we consider that many of these tasks were originally developed for use in young children. Such is the case for false belief tasks, where accurate performance depends on the appreciation that others can hold inaccurate beliefs (Gopnik &

Astington, 1988; Perner & Wimmer, 1985; Wimmer & Perner, 1983), and tasks that involve cartoons depicting the consequences of physical, emotional and intentional actions (Baron-Cohen et al., 1986). Further than this, some mentalising tasks were initially developed for use in non-human animals, to determine not the nature of mentalising but simply whether nonhuman primates such as chimpanzees show evidence of the ability to mentalise (Premack & Woodruff, 1978). Given such history, it is unsurprising that adults show ceiling levels of performance on many of these tasks.

The RMET is often described as assessing mentalising and shows a good level of variability within even healthy adults (As shown in chapter 2), yet, consistent with the discussion of mentalising in chapter 1, the RMET is not a good assessment of the elements of mentalising that are of interest here. As shown and discussed in Chapter 2, RMET performance shows a high level of correlation with facial emotion perception tasks and may be best described as an emotional labelling task (Oakley et al., 2016). Consistent with its inclusion in the previous chapter, this task is far more akin to the "affective empathy" component of the two-stream model than to the cognitive empathy component. Indeed, the RMET has been described as an index of mental state *decoding* as opposed to mental state *reasoning* (Dodell-Feder, Lincoln, Coulson, & Hooker, 2013). Tasks assessing mentalising through text-based stories has potential value as a naturalistic and sensitive way to assess of individual differences in mentalising in healthy adults. Experiences communicated through written language, however, sit entirely within the domain of the cognitive component of social cognition (Tager-Flusberg & Sullivan, 2000). Written words are devoid of perceptual social and emotional content and as such, social information must be conceptually constructed. Indeed an interrelationship has been proposed between language and TOM (de Villiers, 2007; Hale & Tager-Flusberg, 2003; Strickland, Fisher, Keil, & Knobe, 2014) and the important role of language in mentalising is supported by studies showing delays in mentalising ability in deaf children who learn to sign late relatively late (Petersen, Roberts, Knopman, & et al., 2009; Peterson, Wellman, & Liu, 2005; Wellman, Fang, & Peterson, 2011).

Building on existing work, the purpose of this study was to investigate the relationship between microstructural properties of the anterior CB and mentalising abilities in healthy adults. I hypothesised that in healthy adults the anterior portion of the CB, the subgenual CB, would show a relationship with performance on mentalising tasks. For this purpose I utilised a performance-based text-based measure of mentalising designed for use in a healthy adult population, the short

story task (SST) (Dodell-Feder et al., 2013). A performance-based measure was used because individuals' judgements of their own mentalising ability tends to be inaccurate, individuals giving higher judgements of their own mentalising ability than ratings given by others (Eslinger et al., 2011). The SST was developed to overcome the limitations of many existing mentalising assessments and enable the assessment of individual differences in mentalising in healthy adults. The SST was designed to assess mentalising using naturalistic stimuli which require participants to utilise contextual information and to make judgments based on a variety of mental and emotional states, both complex and simple (Dodell-Feder et al., 2013). This task capitalises on the ability of stories to stimulate individuals to automatically mentalise without the need to present any perceptual information such as facial expression. Reading stories that involve mental states have been shown to activate cortical regions associated with mentalising even when it is not required for task completion (Dodell-Feder et al., 2011; Fletcher et al., 1995; Koster-Hale & Saxe, 2011; Tamir, Bricker, Dodell-Feder, & Mitchell, 2016). Indeed, evidence suggests that reading non-fiction stories may be related to better mentalising (Kidd & Castano, 2013; Mar, Oatley, Hirsh, dela Paz, & Peterson, 2006; Tamir et al., 2016). The absence of any perceptual information in a text-based story task allows for assessment of mentalising independent of the effect of perception. As such it can be seen as a relatively pure assessment of "cognitive empathy".

As in chapter 2, I will investigate the relationship between CB microstructure and SST performance utilising of DWI and white matter tractography. As in chapter 2, I will use HARDI and CSD in an attempt to maximise the anatomical accuracy of the tracts of interest and will consider the FA of the tracts in relation to task performance.

3.2 Method

3.2.1 Participants

Forty-nine healthy adults underwent DWI and completed a short battery of cognitive tasks, including the SST (detailed below). The CB could not be adequately reconstructed in two participants and these individuals were therefore excluded from further analysis. The final analysis thus included forty-seven individuals (aged 18-34 years, M=24.2±3.9 years; 13 males). All participants provided written informed consent prior to participation. The study was conducted in line with the Declaration of Helsinki and was approved by the Cardiff University School of Psychology Research Ethics Committee.

3.2.2 Image Acquisition & pre-processing

Whole –brain DWI data were acquired at the Cardiff University Brain Research Imaging Centre (CUBRIC) according to the same acquisition and pre-processing protocol outlined in Chapter 2.

3.2.2.1 Tractography

Deterministic tracking was performed in native diffusion space, utilising CSD to overcome issues in the diffusion tensor model that result in unreliable predictions of fibre orientation in voxels containing crossing fibres (Tournier et al., 2008; Tuch et al., 2002). CSD was used to extract fibre orientation information in each voxel with spherical harmonics order set to no higher than lmax = 6 (Tournier et al., 2004). Tracking was performed using every voxel as a seed-point using a step size of 0.5mm and an angle threshold of 60˚ to prevent the reconstruction of anatomically implausible fibres. Once whole-brain tractography was complete, ROIs were used to "virtually dissect" the three components of the CB as described below.

3.2.2.2 Cingulum Bundle (CB)

The CB has three basic components: subgenual, retrosplenial (or dorsal), and parahippocampal (or temporal) (Heilbronner & Haber, 2014; Jones, Christiansen, et al., 2013) (see Figure 3.1). Three-dimensional reconstruction of the three CB components for each hemisphere was performed using a multiple ROI approach. ROIs were manually drawn in native space on color-coded fibre orientation maps (Pajevic & Pierpaoli, 1999), using landmark techniques as previously used and shown to be highly reproducible (Catani & Thiebaut de Schotten, 2008; Metzler-Baddeley et al., 2011; Wakana et al., 2007; Yasmin et al., 2008). Components of the CB were delineated according to a previously described protocol (Jones, Christiansen, et al., 2013).

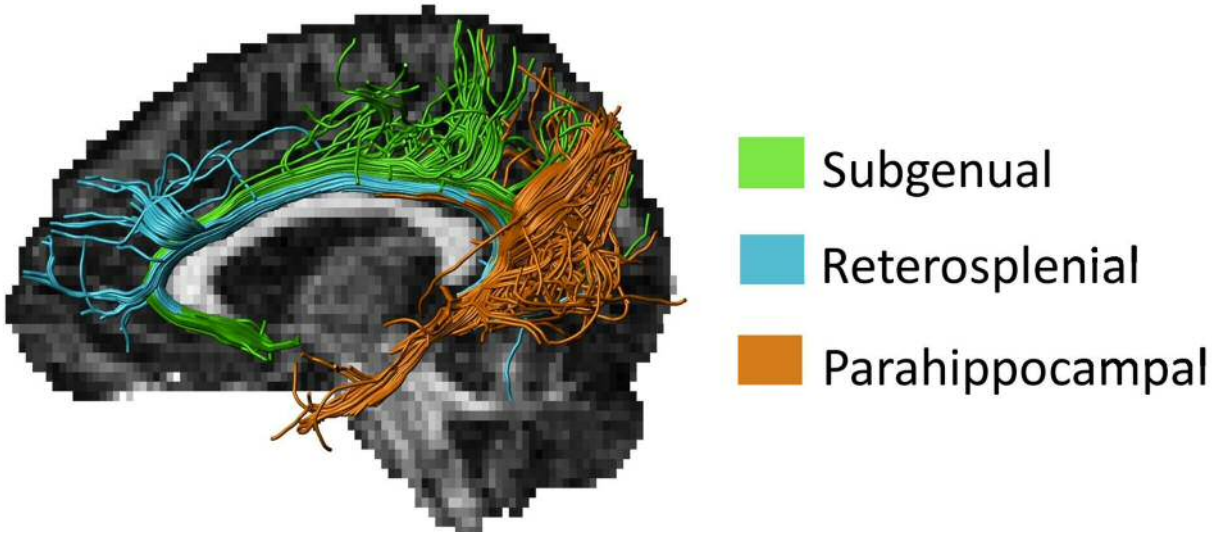

Figure 3.1. Example reconstruction of the CB in one participant. Fibres are colour coded according to CB component: Green = Subgenual; Blue = Retrosplenial; Orange = Parahippocampal

3.2.2.2.1 Subgenual

The subgenual CB was isolated using two AND ROIs, one placed on a coronal slice three slices posterior to the most anterior part of the genu of the CC and the second was placed on a coronal slice five slices anterior to the midpoint of the CB (See Figure 3.2).

3.2.2.2.2 Retrosplenial

The retrosplenial CB was isolated using an AND gate placed around CB fibres on a coronal slice located five slices posterior to the midpoint of the CB and another AND gate placed around CB fibres located on an axial slice three slices above the most ventral plane of the splenium (See Figure 3.2).

3.2.2.2.3 Parahippocampal

The parahippocampal CB was isolated using the restricted protocol outlined in Jones et al (2013). The restricted protocol was used to ensure that projections to the anterior portions of the CB were excluded ensuring greater separation of the different CB components. Two AND gates were placed, the first was in the same location as the gate outlined for the retrosplenial CB located on the axial plane and the second was located on a slice four slices ventrally to the first. To obtain a restricted reconstruction an additional NOT gate was placed in the location of the coronal AND gate outlined for the retrosplenial CB reconstruction (See Figure 3.2).

Tractography was carried out for the LH and RH separately and for each tract an additional NOT gate was placed on a sagittal slice located between the two cerebral hemispheres to ensure that only fibres from the hemisphere of interest were included. The resulting tract masks were intersected with the voxel-wise free-water corrected whole-brain maps of FA and mean FA values for each CB component in each hemisphere were calculated.

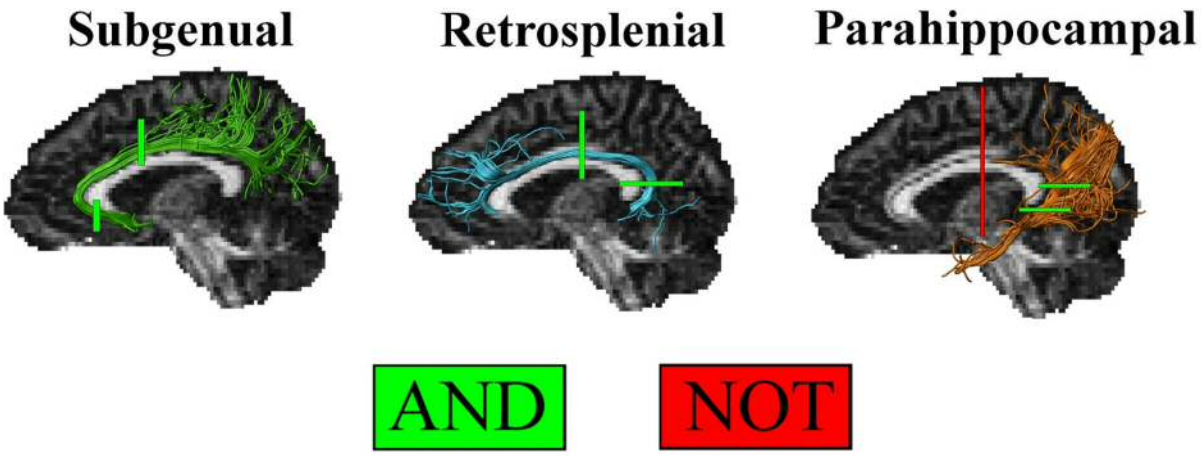

Figure 3.2. Example reconstruction of the subgenual, retrosplenial and parahippocampal segments of the CB. Waypoint regions-of-interest (ROIs) used for reconstructing each tract are shown. Green=And; Red=Not.

3.2.3 Tasks and procedure

3.2.3.1 Short Story Task (SST)

The SST (see Dodell-Feder et al. (2013) for full description) involves participants reading a short fictional story, *The End of Something*, by Ernest Hemingway and answering a series of 14 questions designed to assess explicit mental state reasoning and comprehension of non-mentalistic components of the story.

The End of Something, opens with a description of the demise of an old lumbering town and then follows a pair of protagonists (Nick and Marjorie) during an evening fishing trip. During the trip the interaction of the protagonists becomes increasingly tense and it becomes evident that while Nick and Marjorie are in a relationship, Nick is dissatisfied and wishes to end the relationship. The story was selected by Dodell-Feder et al (2013), as the mental and emotional states of the characters are not explicitly described and as such, their thoughts, feelings and intentions must be inferred from their actions and contextual information provided within the story. The story was further selected due to its relatively clear writing style and simple language, which minimises the influence of language comprehension abilities on task performance (Dodell-Feder et al., 2013).

After reading the story, participants are asked a series of questions. Eight questions probe explicit mental state reasoning regarding the story characters' mental states and five questions probe comprehension of the non-mentalistic components of the story. Responses are scored according to a standardised rubric in which responses are given a score of 0, 1, or 2, with higher scores given for answers showing more complex mental state inference or more detailed memories and comprehension of the story. From these responses, separate performance scores are obtained for mental state inference (SST-M) (with scores ranging from a minimum of 0 to a maximum of 16) and comprehension (SST-C) (with scores ranging from 0 to 10). An example mental state question is "Why does Marjorie sit with her back toward Nick when she asks, "Isn't love any fun?" An example comprehension question is "Nick and Marjorie have a pail of perch for what purpose"? Dodell-Feder et al. (2013) found that the SST is sensitive to variation in mentalising ability in healthy adults, can be reliably scored, and shows concurrent validity with other measures of social cognition.

3.2.3.2 National Adult Reading Test-Revised (NART)

The National Adult Reading Test-Revised (NART) (Nelson, 1982) was used as a control measure of verbal experience, for which it has been shown to have high construct validity (Crawford, Stewart, Cochrane, Parker, & Besson, 1989) The test involves participants reading aloud a series of irregularly pronounced words that do not have the grapheme-phoneme correspondence usually found in the English language (e.g. "*pint*"). Participants are marked for the number of incorrect responses (from a total of 50 words) and as such lower scores indicate higher levels of ability.

3.2.4 Statistical Analysis

Exploratory data analysis was carried out to assess normality in data distribution and check for outliers. No variables diverged substantially from normality bar the SST-C, which showed a negative skew. Therefore, parametric analyses were carried out for most analyses and non-parametric analyses were carried out for analyses including the SST-C. Two-tailed Pearson's correlation coefficients were calculated to determine the relationship between individuals' mean FA values for each CB component and task performance. We also report nonparametric Spearman rank-order correlation coefficients as appropriate.

To control the family-wise error rate, for each of the two SST measures (SST-C and SST-M), correlations with FA were Bonferroni corrected by dividing the 0.05 alpha level by the number of statistical comparisons (Three CB components across two hemispheres) i.e. p = 0.05/6 = 0.0083. For the statistical comparison of dependent correlations, a directional Steiger Z-test (Steiger, 1980) was used, as implemented in the online calculator of Lee and Preacher (2013) (http://www.quantpsy.org/corrtest/corrtest2.htm).

In line with the recommendations of Dienes and Mclatchie (2017), complementary default JZS Bayes Factors were computed for each *p* value, reported here with unidirectional priors (BF_{10}) (Wetzels & Wagenmakers, 2012). For non-parametric analyses, BFs are for Kendall Tau not Spearman rho.

3.3 Results

3.3.1 Behavioural performance

Performance on the SST-M items was in line with that reported in the original paper (Dodell-Feder et al., 2013), though the mean score in our sample was slightly higher, showed a normal distribution and slightly more variability (M=9.4.6±3.1). Performance on the SST-C items was slightly lower than that reported by the original paper with several individuals scoring below scores reported previously (M=7.7±2.1) (Dodell-Feder et al., 2013). The mean number of NART errors was 18.8±5.4.

No significant correlation was observed between performance on the SST-M and SST-C items (r=0.187, p=0.208, BF_{10}=0.392, 95% CI = -0.106, 0.450, r_s=0.181, p=0.224, BF_{10}=0.472, 95% CI = -0.060, 0.317), indicating that performance on the SST-M was not driven by basic comprehension abilities. Furthermore, there was only a modest, statistically non-significant correlation between NART errors and SST-M performance (r=-.275, p=0.065, BF_{10}=0.963, 95% CI = -0.511, 0.018). A significant correlation was however seen between SST-C performance and NART errors (r=-.359, p=0.014, BF_{10}= 3.356, 95% CI =-0.575, -0.072, r_s=0.181, p=0.224, BF_{10}=3.655, 95% CI = -0.427, -0.046). Indicating that, in line with Dodell-Feder et al. (2013), while SST-C is related to verbal experience, the explicit mental state reasoning component of the SST is relatively independent of both non-mentalistic story comprehension and verbal experience.

3.3.2 Cingulum Bundle Microstructure

Previous work (Jones, Christiansen, et al., 2013) has shown the different sub-divisions of the CB to have different microstructural properties. To assess whether such a distinction in the microstructure of each component were present here, the mean FA values for each of the three components across the two hemispheres were compared (Bonferroni corrected repeated measures ANOVA). Consistent with previous work, FA was seen to differ across the three tracts of interest (F(2,92)=144.48, p <0.001, BF_{10}=7.4e43). No overall difference was however observed between the two hemispheres (F(1,46)=0.939, p=0.338 BF_{10}=0.149).

		Subgenual		Retrosplenial		Parahippocampal	
		Right	Left	Right	Left	Right	Left
Subgenual	Right	0.355	0.113	0.252	0.376**	-0.013	0.268
	Left		0.359	0.141	0.315*	0.230	0.051
Retrosplenial	Right			0.425	0.552**	0.342*	0.293*
	Left				0.422	0.184	0.338*
Parahippocampal	Right					0.345	0.559**
	Left						0.338

Table 3.1. Correlation co-efficients for correlations of FA values between CB components. Means for each tract of interest are highlighted and given along the diagonal. *Significant at $p<0.05$, ** significant at $p<0.01$

Analyses were run to determine whether differences in the pattern of data were present across the two hemispheres to determine whether the data justified their separation for further analysis. Consistent with the absence of an observation of a difference across the two hemispheres as a whole, the only tract that was seen to have significantly different FA values between the LH and RH was the parahippocampal CB ($t(46)=2.593$, $p=0.013$, $BF_{10}= 3.129$). Indicating that the other pathways did not differ in their average FA value across the two hemispheres. However, while FA in the LH and RH were seen to be significantly correlated in the retrosplenial and parahippocampal sections of the CB (See Table 1), FA values were not seen to be significantly correlated between the subgenual CB in the LH and RH (See Table 1). This suggests that despite similar overall FA values there is a meaningful difference in pattern of FA values seen across the two cerebral hemispheres in the subgenual CB. As such analyses were carried out for the two hemispheres separately.

It was notable that the left retrosplenial CB was seen to correlate with frontal tracts, while the right retrosplenial CB was seen to correlate with posterior tracts (See Table 1).

3.3.3 Structure-behaviour associations

3.3.3.1 SST-M

Analysis revealed a significant correlation between SST-M scores and FA of the subgenual CB in the LH but not the RH (See Table 2 and Figure 2), such that better mental state reasoning was linked to *lower* FA in the left subgenual CB. Follow-up analyses, utilising directional Bayes factors for the prior hypothesis of a negative relationship between left CB FA and SST-M performance, showed there to be substantial evidence for the presence of a negative correlation between the two (BF_0=11.543, 95% CI = 0.93, 0.111). The negative correlation between SST-M score and subgenual CB FA was significantly stronger in the left than in the RH (z=1.902, p=0.029).

For the retrosplenial and parahippocampal CB, no significant correlations were observed between SST-M scores and FA of these tracts in either hemisphere (See Table 2). Further comparisons additionally showed the correlation between SST-M performance and left subgenual CB FA was significantly different from the relationship seen between SST-M performance and left parahippocampal CB (z=-2.421, *p*=0.008) and left retrosplenial CB (z=-1.875, *p*=0.030) FA. This supports the claim that the observed association with SST-MS was indeed specific to the LH subgenual CB.

					95% CI	
		r	*p*	BF_{10}	Lower	Upper
Subgenual	Right	-.023	.879	0.184	-0.299	0.258
	Left	-.385	.008*	5.797	-0.593	-0.104
Retrosplenial	Right	-.092	.538	0.219	-0.359	0.195
	Left	-.072	.632	0.203	-0.342	0.214
Parahippocampal	Right	.035	.817	0.187	-0.247	0.309
	Left	0.92	.540	0.218	-0.195	0.359

Table 3.2. The relationships between performance on the mentalising component of the short stories task items and fractional anisotropy in the different components of the cingulum bundle.

* Indicates a significant relationship at a Bonferroni corrected P < 0.05

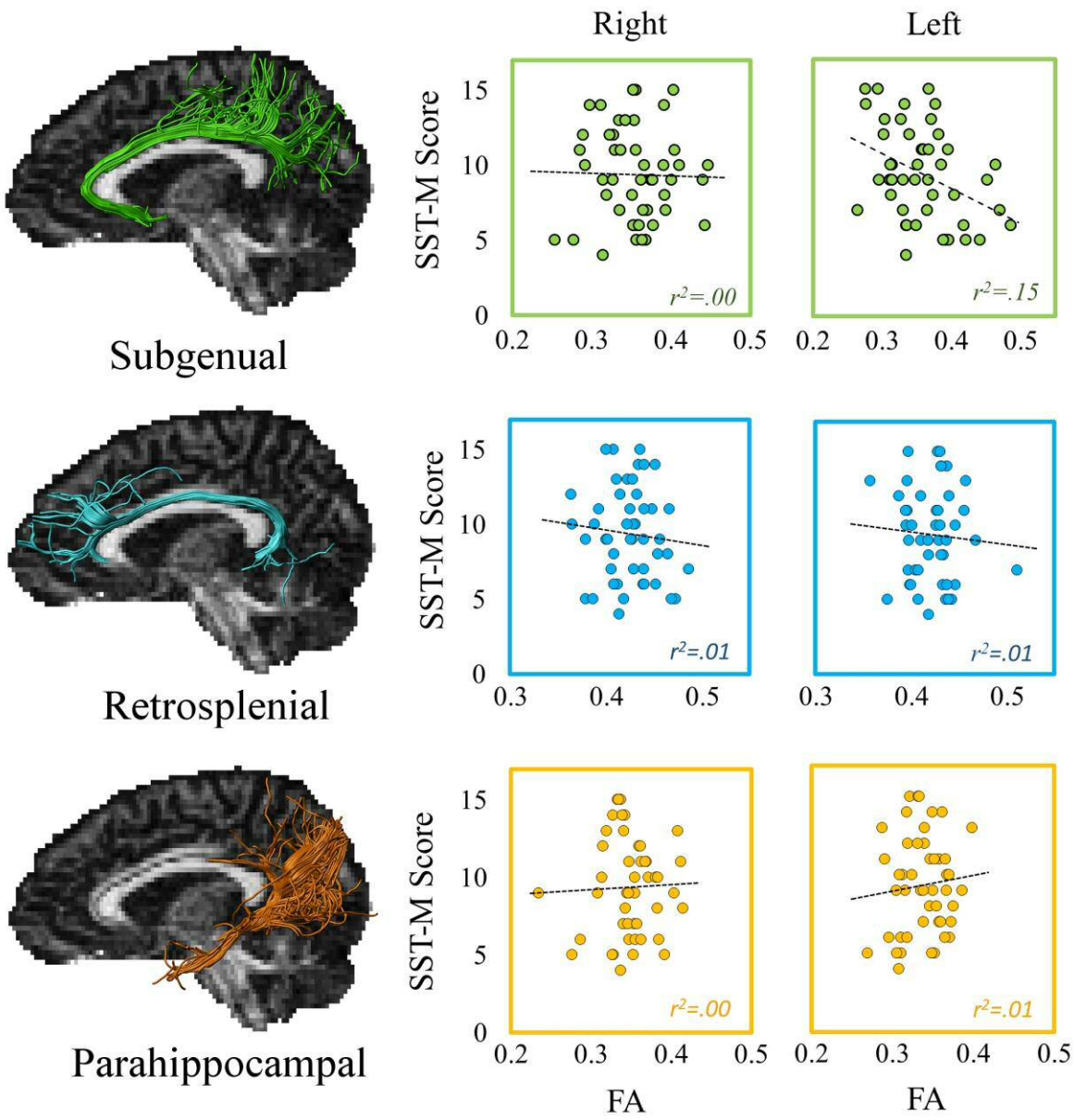

Figure 3.3. The relationship between Fractional Anisotropy (FA) in the subgenual, retrosplenial and parahippocampal CB and explicit mental state reasoning performance on the Short Story Task. SST-M= Metalizing component of the short stories task

3.3.3.2 SST-C and the influence of linguistic experience

No significant correlation was observed between SST-C and FA in either the right (r=0.051, *p*= 735, BF_{10}=0.192, 95% CI =-0.233, 0.323, r_s=-0.072, *p*=0.632, BF_{10}=0.203, 95% CI= -0.224, 0.152) or the left subgenual CB (r=-0.061, *p*=0.682, BF_{10}=0.197, 95% CI= -0.333, 0.223, r_s=-0.068, *p*=0.648, BF_{10}=0.211, 95% CI = -0.234, 0.142). These relationships were seen to be significantly different from those seen between FA in the subgenual CB and performance on the SST-M in the left (z=1.781, *p*= 0.037), but not the right (z=0.385, *p*=0.350). Neither was any relationship seen between NART performance and FA in either the right (r=-0.053, *p*=0.725, BF_{10}= 0.195 95% CI =-0.328, 0.234) or the left subgenual CB (r=0.183, *p*=0.223, BF_{10}=0.377, 95% CI = -0.111, 0.437). Again these were seen to be significantly different from the relationship observed in the left (z=-2.488, *p*=0.006) but not the right (z=0.125, *p*=0.450) hemisphere. This suggests that the relationship observed between LH subgenual CB microstructure and SST-M performance was not driven by an underlying relationship with verbal experience or more general comprehension of the text.

3.3.4 Supplementary analysis

Participants whose data is reported in this chapter completed a battery of tasks that included both the SST and the RMET. Most, though not all, of the individuals included here also provided data to experiment 2 in chapter 2. As such it is possible to run analyses to assess for the presence of a correlational double dissociation between the microstructural properties of the two pathways of interest from chapter 2 and 3 (UF and subgenual CB) and performance on the two of the tasks of interest, the SST-M and RMET.

Consistent with the findings of chapter 2, in the individuals included here, a significant relationship was observed between performance on the emotional items of the RMET and right (r=0.428, *p*=0.003, BF_{10}=14.47, 95% CI =0.153, 0.625) but not left UF microstructure (r=0.027, *p*=0.203, BF_{10}=0.185, 95% CI= -0.254, 0.303). A significant relationship was not however observed between performance on the SST-M and FA in either the right (r=-0.035, *p*=0.814, BF_{10}=0.187, 95% CI=-0.310, 0.247) or left UF (r=0.005, *p*=0.974, BF_{10}=0.182, 95% CI=-0.274, 0.283). Indicating a dissociation of these tasks. Further to this, while a significant relationship was observed between FA in the subgenual CB and SST-M performance (reported above), no significant relationship was

observed between FA in the left (r=0.026, *p*=0.860, BF_{10}=0.185, 95% CI= -0.255, 0.302) or right CB (r=0.146, *p*=0.328, BF_{10}=0.289, 95% CI=-0.143, 0.404) and performance on the emotional items of the RMET. Providing a double dissociation between these tasks and structures.

To determine whether the observed relationships between tracts and tasks were significantly different, Steiger z-tests for correlations with a variable in common were run. As the direction of the difference was expected 1-tailed results are reported. To assess for the differences in the magnitude rather than the direction of relationships, analyses were run for the inverse of SST-M score. The correlation between FA in the right UF and performance on the SST-M was seen to be significantly different from that seen between right UF FA and the emotional items of the RMET (z=2.125, *p*=0.017). The correlation between FA in the left subgenual CB and SST-M was additionally seen to be significantly different from that seen between left subgenual CB FA and the emotional items of the RMET (z=1.914, *p*=0.028), providing evidence of a double dissociation.

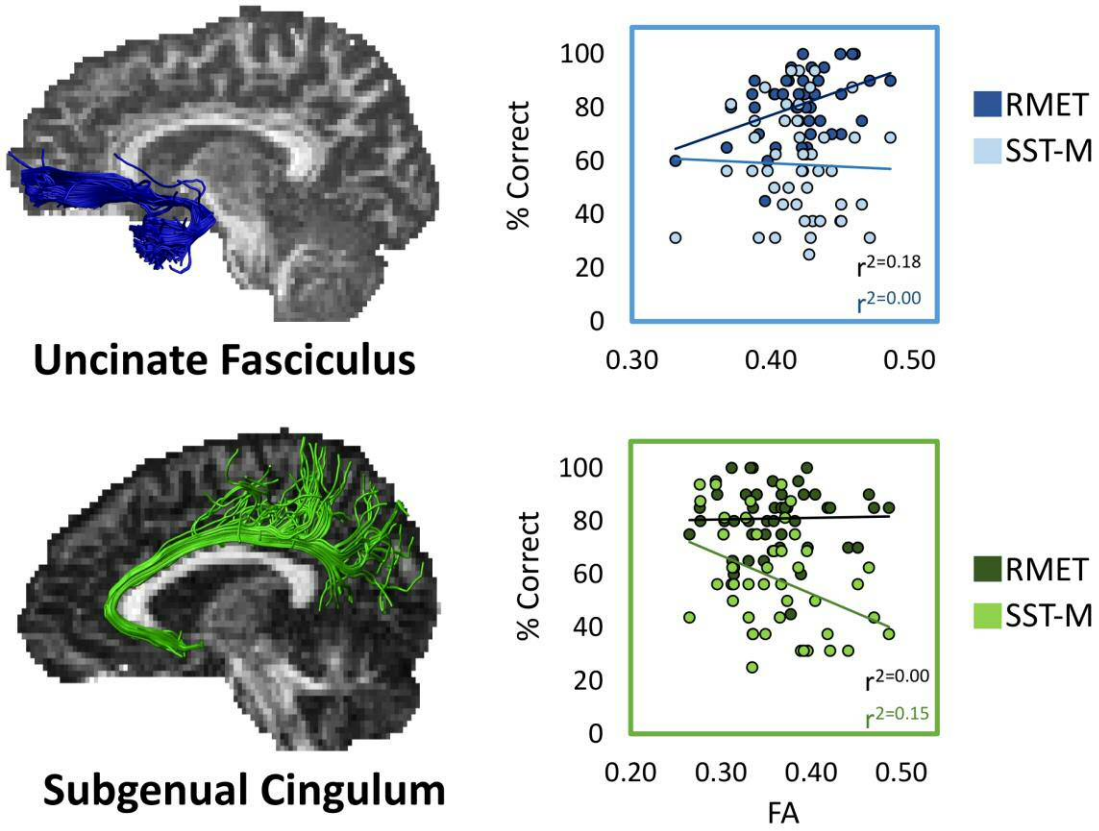

Figure 3.4. Comparison of correlations between tasks of interest in uncinate fasciculus and subgenual cingulum. RMET=Reading the Mind in the Eyes Task; SST-M= Short Stories Task mental state reasoning component; FA= Fractional Anisotropy

3.4 Discussion

3.4.1 Overview

This chapter investigated whether there is evidence that the CB plays a role in mentalising. This was investigated using a novel assessment of mentalising, the SST, a text-based story task, developed to avoid ceiling effects in healthy adults, and show sensitivity to individual differences in mentalising ability (Dodell-Feder et al., 2013). DWI and tractography were utilised to extract white matter microstructural metrics of three posited components of the CB; the subgenual, retrosplenial and parahippocampal CB (Heilbronner & Haber, 2014; Jones, Christiansen, et al., 2013). Of all of the pathways considered, it was found that microstructural properties of the left but not RH subgenual CB were related to performance on mentalising based components of the SST but not components sensitive to non-mental state aspects of story comprehension, nor linguistic experience as assessed with the NART. These findings suggest that the white matter connectivity provided by the subgenual CB has specific a role in supporting mentalising and therefore a role in supporting the neurocognitive network underlying cognitive empathy.

The observation of a relationship between mentalising and the microstructural properties of the left subgenual CB alone highlights the distinguishable roles that the components within the CB may have in supporting cognitive functioning. This is consistent with previous work which has shown both different microstructural properties for each of the components of the CB and different relationships with a range of cognitive functions (Cooper, Thapar, & Jones, 2015; Keedwell et al., 2016; Metzler-Baddeley et al., 2012; Wakana et al., 2007; Jones, Christiansen, et al., 2013; Metzler-Baddeley et al., 2012). These differences in structure-function relationships highlight the importance of separating the CB into these separate pathways, rather than treating it as a unitary tract. Particularly when investigating structure-function relationships. As each has different properties, collapsing across these multiple tracts, will introduce a noise to analyses and may wash out relationships between structural measures and cognitive functions.

The observation of a selective correlation between mentalising based on text-based fiction and the subgenual CB is consistent with existing knowledge regarding the functional role of grey matter regions that are likely connected by this subdivision of the CB. Regions within the mPFC

have consistently been identified as being involved in belief inference (Yoshida et al., 2010) and mentalising, in conjunction with medial parietal regions (Spunt & Adolphs, 2014; Spunt & Lieberman, 2012). Mental state inference as assessed using other story-based tasks, similar to that used here, has also been seen to be associated with vmPFC volume in healthy adults (Lewis, Rezaie, Brown, Roberts, & Dunbar, 2011; Powell, Lewis, Dunbar, García-Fiñana, & Roberts, 2010).

Regarding social cognition, only limited prior work has investigated the relationship between the CB and social cognition and, to my knowledge, no such work has split the CB into the components discussed here. Consistent with this work, research in psychopathy has however shown that, affective detachment appears to be related to white matter microstructural metrics in the anterior but not parahippocampal portions of the CB, in particular in the LH (Sethi et al., 2015). Altered mental perspective taking has also been shown following damage to anterior portions of the CB in glioma patients (Herbet et al., 2015). This association is consistent with the proposition that anterior CB alteration in bvFTD may have a role in the social cognitive symptoms of bvFTD. In line with this, it is anterior portions of the CB which appear particularly sensitive to the presence of bvFTD (Zhang et al., 2009). Yet, despite apparent difference in disease vulnerability across the CB, existing work has not systematically investigated whether FTD affects the three posited portions of the CB differently (Whitwell et al., 2010; Zhang et al., 2009; Zhang et al., 2013). There has also been relatively little consideration of the role that CB alteration may have in the functional symptoms of bvFTD. This results of this chapter suggest that there may be great potential value in conducting such work in the future.

The left lateralisation of the relationship observed here is consistent with previous work. For instance medial regions of the LH show enhanced activity relative to RH regions when individuals are required to determine the intentions of others (Spunt & Adolphs, 2014; Spunt & Lieberman, 2012) or make inferences regarding beliefs (Yoshida et al., 2010).It is also the microstructural properties of the left dorsal CB that have also been related to psychopathy (Sethi et al., 2015). Mentalising may not, however, be entirely lateralised; while disruption of the left CB has been seen to be a strong predictor of low cognitive empathy in glioma patients (Herbet et al., 2015), lesions to the right CB have also been associated with impairments in a high-level cartoon-based mentalising task (Herbet et al., 2014). This indicates that the anterior CB *bilaterally* may have an important role in mentalising. One possible explanation for the lack of association with right CB microstructure reported here, is that the right anterior CB may be subject to greater demands

from cognitive functions other than mentalising. For example, the subgenual CB has previously been implicated in having a role in regulating emotional conflict between perceptual stimuli, including facial emotion expressions (Cooper et al., 2015; Keedwell et al., 2016; Metzler-Baddeley et al., 2012; Wakana et al., 2007). Though not all of this work split the CB by hemisphere, the findings of chapter 2 would suggest that this relationship may be more prominent in the RH.

3.4.2 Executive function

Interestingly, previous work has shown a selective relationship between left subgenual CB microstructure and executive control (Cooper et al., 2015; Keedwell et al., 2016; Metzler-Baddeley et al., 2012; Wakana et al., 2007). Executive control, sometimes called executive functioning is a complex ability that underlies the cognitive control of behaviour and cognitive processing, supporting goal-oriented behaviour. Executive functioning has been discussed as a vital component of empathy (Decety & Jackson, 2004; Decety & Lamm, 2006) and is impaired in bvFTD across a range of tasks (Collette et al., 2007; Possin et al., 2013) even at early stages of disease (Seeley et al., 2008). Indeed executive function impairments are a feature of the diagnostic criteria for bvFTD (Rascovsky et al., 2011). This suggests either that executive function and mentalising could be inter-related, or may both be supported by the subgenual CB and thus affected by structural alteration to the CB.

Evidence for the relationship between executive functioning and mentalising remains mixed however these two processes may be at least partly separable. In bvFTD, evidence for a relationship between executive dysfunction and empathy change has been mixed (Eslinger et al., 2007; Gregory et al., 2002; Lough et al., 2001; Lough & Hodges, 2002; Lough et al., 2006; Snowden et al., 2003; Torralva et al., 2007) though a recent meta-analysis concluded that evidence does not indicate a relationship between the two (Bora et al., 2015). In support of the separability of these functions, in lesion patients, impairments in empathic functioning have been seen in the face of unimpaired executive functioning (Shamay-Tsoory et al., 2009). It is, however, entirely feasible that executive function is necessary for mentalising. Indeed it would make intuitive sense for executive function to be required for mentalising but not the reverse. Despite the potential inter-relationship between these functions, it does however seem unlikely that executive function's relationship with the left subgenual CB drives the relationship observed here, as executive

function has been seen to be positively related to FA in the subgenual CB (Cooper et al., 2015; Keedwell et al., 2016; Metzler-Baddeley et al., 2012; Wakana et al., 2007). Further work is necessary to establish the relationship between these cognitive functions and clarify each of their relationships with the microstructural properties of the subgenual CB.

3.4.3 A role for Von Economo Neurons (VEN) in mentalising?

While it was hypothesised that a relationship would be observed between the microstructural properties of the subgenual CB and task performance it was unexpected that the relationship would be *negative*. Frequently, though not exclusively, improved performance on cognitive tasks is related to higher FA in pathways of interest. Yet, as outlined in Chapter 2, there is currently limited understanding of how DTI measures, such as FA, relate to biological properties of tissue, FA may be influenced by myelination, membrane permeability, axonal number and axonal diameter (Jones, Knösche, et al., 2013). As such while robust, reliable and reproducible associations between microstructural properties of a tract and task performance are of use, biological interpretations, and thus the interpretation of the direction effects, are fraught with difficulty (Jones, 2008; Jones, Knösche, et al., 2013). Importantly though, for the purposes of establishing a relationship between function and structure, they may be unnecessary.

One intriguing possibility for the negative relationship observed here is however worthy of note. As stated, variability in axonal diameter is one established biological variable that influences FA. In the subgenual CB variability in axonal diameter across individuals could occur due to differences in the presence of VEN. VEN are projection neurons with particularly large dendrite and axon diameters (Allman et al., 2002; Allman et al., 2011; Nimchinsky et al., 1995) which have been proposed to be involved in complex social behaviour, the rapid processing of social information (Allman et al., 2010; Allman et al., 2005; Butti et al., 2013) and the relaying of signals to cortical regions involved in mentalising (Allman et al., 2005).

Though the sites to which VEN project have not yet been determined the regions in which they have been identified closely match the path of the subgenual CB (Allman et al., 2002; Allman et al., 2010). Indeed VEN project into the CB, with high numbers found particularly in subgenual regions (Nimchinsky et al., 1995). If VEN facilitate fast communication between regions involved in mentalising then increased numbers of VEN would facilitate performance on mentalising tasks, such as the SST. In this case, individuals with increased numbers of VEN would show better performance on mentalising tasks, but because of the VEN's unusually large axonal diameter, would have lower FA within the subgenual CB (see Figure 3.4). Larger axons would result in lower FA as they would pose fewer barriers to diffusion perpendicular to the orientation of the fibre, but may facilitate faster signal transmission between cortical regions between which they project (Takahashi et al., 2002). Unfortunately, work directly investigating VEN requires histological work, limiting the ability to investigate the role that these specialised neurons may have in supporting mentalising. The use of advanced diffusion imaging methods that allow for the estimation of axonal diameter (Assaf, Blumenfeld-Katzir, Yovel, & Basser, 2008; De Santis, Drakesmith, Bells, Assaf, & Jones, 2014; Sepehrband, Alexander, Kurniawan, Reutens, & Yang, 2016), may however enable future work to establish whether axonal diameter in the left subgenual CB does indeed relate to mentalising ability.

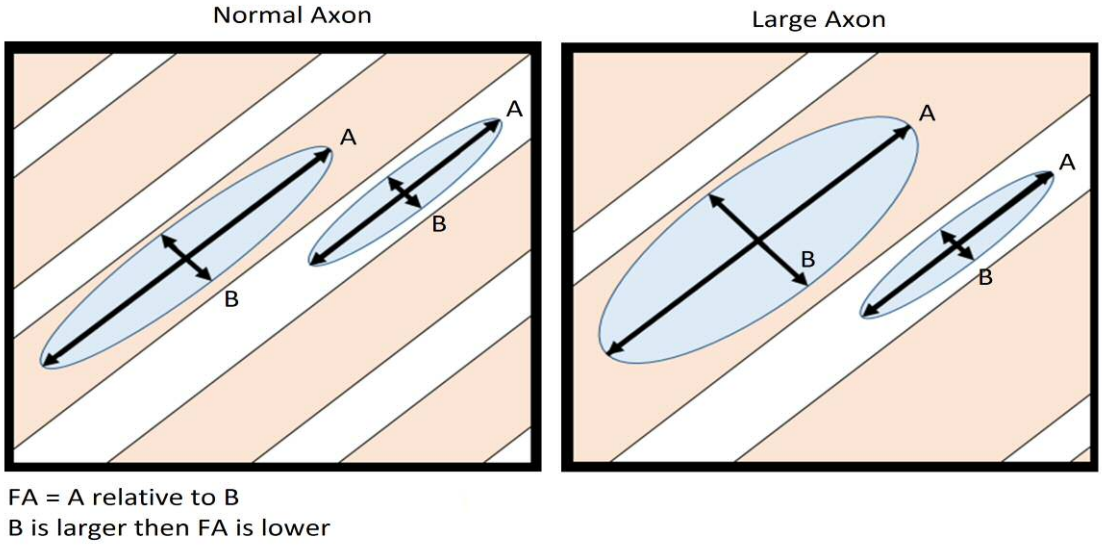

Figure 3.4. Graphical representation of why white matter including axons with greater diameter would result in a lower Fractional anisotropy. FA= Fractional anisotropy

3.4.4 Future directions

Contextual processing may feasibly have a substantial impact on the association observed between microstructural properties of the subgenual CB and mentalising. In the SST, participants are provided with no information about the characters within the story and have only the character's actions with which to infer intentionality and mental state. These inferences about mental state thus critically rely on the integration of contextual information with the participant's existing generalisable knowledge about human actions, intentions and emotions. This context processing may both be important in the ability to infer intention to others and may rely on the subgenual CB. Difficulties in context interpretation have been seen in clinical groups who show CB alterations and difficulties in mentalising, such as children with ASD (Cummings, 2015) and individuals with FTD (Baez et al., 2014; Ibanez & Manes, 2012). Indeed difficulty in processing contextual cues has been argued to have a role in the cognitive empathy deficits in seen in bvFTD (Baez et al., 2014). The CB could have a role in contextual processing, though it is posterior cingulate connectivity that has been seen to have a role in engagement with our external environment (Herbet et al., 2014). This work did not assess context processing or the ability to integrate context and the actions of targets, as such it cannot speak to the impact that context processing may have the relationships observed. To address the role of context processing in the relationship between the subgenual CB and mentalising further work is necessary to establish the extent to which context processing abilities underlie the observed relationship.

As highlighted in Chapter 1, the CB is particularly affected in bvFTD (Agosta, Scola, et al., 2012; Daianu et al., 2016; Mahoney et al., 2014; Whitwell et al., 2010) and prominent impairments in mentalising are seen in FTD (Eslinger et al., 2011; Rankin et al., 2005). The results of the work presented here suggests that alteration in the anterior CB in FTD may underpin inter-individual differences in mentalising. Further work is needed, however, to establish the validity of this proposal. Firstly, despite this apparent difference in disease vulnerability across the CB, existing work has not investigated the three posited tracts separately (Whitwell et al., 2010; Zhang et al., 2009; Zhang et al., 2013) and future work is needed to verify the CB sub-tract in which greatest alteration is observed in FTD. Moreover, studies similar to the one reported here are necessary to establish the relationship between with matter microstructural properties of the CB and

performance on mentalising tasks in FTD. Longitudinal work would be of particular use to establish whether change in white matter is related to change in mentalising.

3.4.5 Dissociation of cognitive components of empathy

Cognitive and perceptual components of empathic functioning have been argued to be dissociable (Blair, 2005, 2008; Cox et al., 2012). In healthy adults functional brain imaging using EEG has shown a temporal dissociation in the processing of face-based perceptual emotion information and story-based contextual information on pain (Sessa, Meconi, & Han, 2014) while lesion work has provided compelling evidence of a double dissociation between these posited components of empathy (Hillis, 2014; Shamay-Tsoory et al., 2009). Consistent with the findings given here, principally left-sided medial frontal lesions have been associated with cognitive empathic deficits while right-sided lateral frontal and temporal lesions have been associated with affective or perceptual empathic deficits (Hillis, 2014; Shamay-Tsoory et al., 2009). In support of the dissociation of these functions, amygdala and OFC lesions have been associated with impaired face based learning but intact cognitive empathy and mental state inference (Hurlemann et al., 2010; Hynes et al., 2006). While work in glioma patients has previously shown that the CB does not have a role in affective empathic processing as anterior CB lesions have been shown to not affect MITE task performance (Herbet et al., 2014).

Though lesion work shows a double dissociation between the two functional components of empathy, there remains relatively limited insight into the specific structural networks involved in each. Though white matter damage may play a notable role in empathic functioning, its potential role is relatively neglected in much lesion work (Leigh et al., 2013; Shamay-Tsoory et al., 2009; Shamay-Tsoory, Tomer, Goldsher, Berger, & Aharon-Peretz, 2004). This is despite the fact that lesion work often involves individuals with traumatic brain injury (TBI). In TBI white matter damage is frequently present beyond observed lesions (Chelly et al., 2011; Mierzwa, Marion, Sullivan, McDaniel, & Armstrong, 2015); Skandson et al 2010) and prominent empathy impairment is often present (de Sousa et al., 2011; Wood & Williams, 2008). Yet, work in TBI has reported little apparent relationship between this and obvious with injury severity (de Sousa et al., 2011). Though minimal work has investigated the role of white matter damage in such empathy alteration it seems feasible that it may well have a key role as diffuse white matter damage is

under-reported in TBI (Sharp & Ham, 2011; Shenton et al., 2012) and appears related to cognitive impairments (Kinnunen et al., 2011; Warner et al., 2010). The absence of a consideration of white matter alteration in such cases therefore means that it provides relatively little information about the specific neural networks that are perturbed to lead to functional empathic change and thus which underlie the functions of interest.

A major difficulty with lesion work is that it is often hard to draw connections between specific brain regions or structures and functions. In many cases lesions are caused by traumatic injury or stroke and as such may be relatively non-specific. For example in the work of Shamay-Tsoory (2009), affective empathy impairments were associated with lesions to a relatively large area of lateral frontal lobe though not confined to grey matter. This makes it hard to determine the relative contribution of different structures within the lesion site to functional impairments of interest. The evidence of a dissociation between specific white matter structures and cognitive components of the two empathic systems provided here both supports the proposition that white matter has a key role in separately supporting these two functions and that white matter structure in healthy adults

3.4.6 Conclusion

The results of the current study support the proposal that the subgenual CB plays an important role in supporting mentalising and suggests a potential role for the anterior CB in supporting cognitive empathic processing. Here I proposed that the negative relationship observed between task performance and microstructural properties of the anterior CB could be due to the presence of VENs within the CB. These neurons, while potentially facilitating the processing of context-relevant social information, would decrease FA of the white matter pathways in which they lie due to their large axonal diameter. As mentalising is posited to have a key role in cognitive empathy (Shamay-Tsoory, 2011; Shamay-Tsoory et al., 2009), the results of this study suggest that there may be a key role for the CB in supporting cognitive empathic processing, consistent with previous reports that damage to the left CB is related to impairment in cognitive empathy (Herbet et al., 2015). While this work provides an initial indication of the importance of the anterior CB in cognitive empathic processing and a possible role for social cognitive change in FTD, further work is necessary to further explore these proposals.

4

Cognitive and perceptual components of empathy in bvFTD: Implications for Dissociation and Diagnosis

4.1 Introduction

As discussed previously in chapter 1, there appears to be a selective vulnerability in bvFTD of large scale neurocognitive networks involved in social cognitive functioning, and the white matter structures that support them (Mahoney et al., 2014; Santillo, Mårtensson, et al., 2013; Seeley et al., 2009). This network-level vulnerability makes bvFTD an ideal model for understanding the role that these networks have in supporting cognitive components of social cognitive functioning. It also suggests that neuropsychological assessments that are sensitive to such network level functioning may be diagnostically useful in bvFTD.

Improving the early detection of dementia is a key goal for science and medicine. Obtaining accurate diagnosis can come as a relief for families (van Vliet et al., 2011) and though there are currently no treatments for FTD, diagnosis and accurate identification of an individual's clinical phenotype is necessary for future planning. Providing support and allowing individuals with FTD and their families to accept and adapt to their new roles (de Vugt & Verhey, 2013). From a research perspective, early detection is important for improving our understanding of the natural history of disease, which is necessary for developing interventions and treatments. Early diagnosis is also of value as studying dementia in its early stages provides the possibility to research the cognitive and behavioural effects of relatively subtle perturbations to neurocognitive systems.

Despite its importance, accurate diagnosis of bvFTD can be a challenging and drawn out process. The time between symptom onset and diagnosis in bvFTD can be around 6.4 years for early onset cases and 3.3 years in those over the age of 65 (van Vliet et al., 2013). As such,

understanding of the very early stages of disease remains limited. This delay in diagnosis may in part be due to bvFTD's primarily social symptoms, as behavioural changes may be inaccurately attributed to other social or psychological factors (Paton, Johnston, Katona, & Livingston, 2004) or not be taken seriously by GPs (van Vliet et al., 2011). There is also considerable symptomological crossover between bvFTD and common psychiatric conditions (Lanata & Miller, 2016; Manes et al., 2010). This means that when individuals do present to health care professionals it may often be in a mental health setting, and as such, individuals with bvFTD frequently receive initial diagnoses of psychiatric conditions, such as schizophrenia or depression (Hsiung et al., 2012; Piguet et al., 2011; Sommerlad, Lee, Warren, & Price, 2014).

The diagnosis of bvFTD heavily relies on accurate behavioural phenotyping thanks to the mismatch between genetics, pathology and clinical presentation in FTD (discussed in chapter 1). As such, understanding the behavioural symptoms of bvFTD is crucial. Yet, this can be a challenge, as there are few clinically accepted assessments of social, empathic or behavioural dysfunction and, despite the presence of profound behavioural alteration, individuals with bvFTD frequently show normal performance on standard dementia assessments and clinical neuropsychological tests (Mendez, Shapira, McMurtray, Licht, & Miller, 2007). Diagnosis thus relies on clinicians accurately identifying relevant symptoms, something that is often dependent upon the clinician's understanding of bvFTD and having experience with its behavioural symptoms. Though this may not be a problem at specialist centres, it can be an issue in non-specialist clinics, where the rarity of bvFTD may mean that clinicians may have limited experience of the condition. A lack of knowledge of bvFTD may particularly, result in a neglect of behavioural symptoms during diagnosis, leading to individuals with bvFTD being missed and individuals without bvFTD being given a bvFTD diagnosis. In one study almost a quarter of individuals diagnosed with bvFTD had autopsy confirmed AD pathology (Mendez, Joshi, Tassniyom, Teng, & Shapira, 2013). Consistent with this occurring partly due to a lack of focus on, or assessment of, social changes during diagnosis, these inaccurately diagnosed individuals showed greater memory problems and fewer changes in personality and judgement than those with FTLD pathology.

There is thus great potential value in assessments that are selectively sensitive to cognitive changes in bvFTD. Assessments of specific components of empathic cognition may have particular clinical value, as empathy change is one of the six behavioural symptoms listed

within the diagnostic criteria for bvFTD (Rascovsky et al., 2011), and one for which there are currently no standardised clinical neuropsychological assessments. Such assessments may additionally aid in improving our understanding of the cognitive changes that occur in bvFTD, which may further aid in diagnosis. Given the apparently selective, network-level degeneration seen in bvFTD (Seeley et al., 2009), assessments that are specific to the cognitive functions supported by these networks seem likely to be particularly sensitive to disease presence.

BvFTD may impact on the neurocognitive networks supporting both cognitive and perceptual empathising. Consistent with the findings of the previous two chapters, cognitive and perceptual empathic functioning are thought to depend on distinct though overlapping neural systems (Tager-Flusberg & Sullivan, 2000). Both of these systems may alter in bvFTD, cognitively (Bora et al., 2015; Janine Diehl-Schmid et al., 2007; Gregory et al., 2002; Henry et al., 2014; Kipps & Hodges, 2006; Kumfor & Piguet, 2012; Lough et al., 2006; Rosen et al., 2002) and (based on evidence of the white matter pathways that may be involved in each from the previous two chapters) neurally (Lam et al., 2014; Mahoney et al., 2014; Whitwell et al., 2010; Zhang et al., 2009; Zhang et al., 2013). Cognitive assessments that are selectively sensitive to the separate components of empathic cognition may therefore have potential to be both sensitive to the presence of bvFTD and be clinically useful. They may also be useful for developing our understanding of the nature of these empathic neurocognitive networks.

Ecologically valid assessments of cognitive components of empathy may have value for the detection of bvFTD. Yet while cognitive components of empathic functioning have previously been discussed in relation to bvFTD (Dermody et al., 2016; Eslinger et al., 2011; Oliver et al., 2015), relatively few studies have used ecologically valid assessments. This is particularly the case for cognitive empathic functioning for which many studies have used informant reports using the IRI (Eslinger et al., 2011; Rankin et al., 2006; Rankin et al., 2005) or performance-based assessments, which lack ecological validity due to involving entirely prescriptive assessments involving Likert-style ratings of intentionality (Baez et al., 2014), or expression labelling (Oliver et al., 2015). None of these assessments therefore bare much resemblance to everyday, dynamic, unprompted mentalising.

Further to the lack of ecologically valid assessments, many assessments do not sub-divide empathy into components consistent with theoretical sub-divisions of empathy. Some work,

for example, equates affective empathy with empathic concern (Baez et al., 2014) or assesses cognitive empathy with a facial expression labelling task (Oliver et al., 2015). Conflating cognitive empathy with perceptual components of empathy. Thus while such assessments provide useful information regarding the presence of empathy-related changes in bvFTD, they do not provide the specificity in cognitive assessment necessary to allow for the consideration of specific neurocognitive networks. There is thus a need within the literature thus for performance-based assessments of specific cognitive components of empathic functioning.

A moderate amount of literature is present regarding perceptual components of empathy in bvFTD, particularly regarding facial emotion comprehension, though it has not been explicitly discussed in the context of perceptual empathy. As discussed in Chapter 2 deficits have been seen on facial emotion labelling tasks such as the Ekman faces (Janine Diehl-Schmid et al., 2007; Keane et al., 2002), emotional hexagram (Buhl et al., 2013), TASIT (Kipps et al., 2009; Shany-Ur et al., 2012) and RMET (Bora et al., 2015; Gregory et al., 2002; Torralva et al., 2007; Torralva et al., 2009). Though, as discussed in Chapter 2 and 3, The RMET includes cognitive state labelling as well as emotional state labelling, posing issues for the classification of the task as a whole, most of these tasks are relatively specific assessments of emotion perception and decoding. Issues are however present concerning assessments of cognitive empathy or mentalising. There have been few ecologically valid, sensitive assessments of mentalising used to assess cognitive empathic functioning in bvFTD. As discussed in chapter 3, most assessments of mentalising that have been used in the field of bvFTD, as with the field in general (Apperly, 2013), have been those originally designed for use in children (Fernandez-Duque et al., 2010; Henry et al., 2014; Le Bouc et al., 2012; Lough et al., 2001; Lough & Hodges, 2002). As outlined in chapter 3, the SST is one assessment that may overcome some issues with mentalising assessments and be a sensitive, ecologically valid assessment for mentalising in bvFTD.

Here I present a pilot investigation of the SST as an assessment for identifying impairment in mentalising in bvFTD. I will present data from a high functioning individual at a relatively early stage of bvFTD regarding performance on tasks sensitive to the previously discussed neurocognitive components of empathy. An individual early on in disease progression is reported to allow for a consideration functional impairment at a relatively early stage of disease, where functional change may be relatively less profound and where differences in the pattern of impairment across neurocognitive systems may be present. As impairment was

expected to be relatively more subtle than that seen in later stages of disease, tasks sensitive to subtle variability in functioning, reported in the previous two chapters, were utilised. These tasks were used as they showed good variability and non-ceiling and non-floor performance in healthy adults. Thus, an assessment of face-based emotion processing (RMET) and text-based mental state inference (SST) were used, each established to be sensitive to dissociable neurocognitive systems. This allows us to consider the impact of bvFTD on specified neurocognitive systems.

4.2 Method

4.2.1 Case History

NB, a lawyer who ran his own legal practice, presented at the Bristol Brain centre in 2014 aged 62. At initial presentation he reported speech errors, word retrieval problems and difficulty remembering names, as well as periods of confusion and disorientation.

At follow up in 2015, NB and his wife reported progressively declining cognition and personality change. He reported depression and suicidal ideation and felt that he was increasingly making decisions that were 'not right', particularly in relation to finances. He was becoming far less social and occasionally felt a proclivity towards violence, a marked change from before. Though he was still running a successful business he was becoming increasingly aggressive, hitting the desk at work, leading to colleagues warning him that they would move is staff if he continued, for their own safety. He reported difficulties recalling the names of clients and described having to claim that his secretary had not provided him with the correct names when he made errors. NB was eager to obtain a diagnosis or explanation for his difficulties due to the need to plan for his future and the future of his company.

In the autumn of 2015, NB was diagnosed with probable bvFTD on the basis of behavioural change, progressive functional deterioration and progressive SPECT alteration. At the point of diagnosis he scored 20/30 on the Montreal cognitive assessment (MOCA)(Nasreddine et al., 2005).

4.2.1.1 Neuroimaging

In 2014 single-photon emission computed tomography (SPECT) imaging on NB showed reduced perfusion in the left inferior frontal and inferior parietal lobes. Medial parietal perfusion was noted to be preserved. Follow-up assessments were carried out in 2015 and structural MRI was reported to be normal for NB's age with no focal atrophy being apparent, including none in the frontal and temporal lobes. In line with results from 2014, SPECT imaging suggested the presence of alteration in perfusion in the frontal and parietal lobes. This was seen to be more extensive than that which was present in 2014 and alterations were less clearly left lateralised.

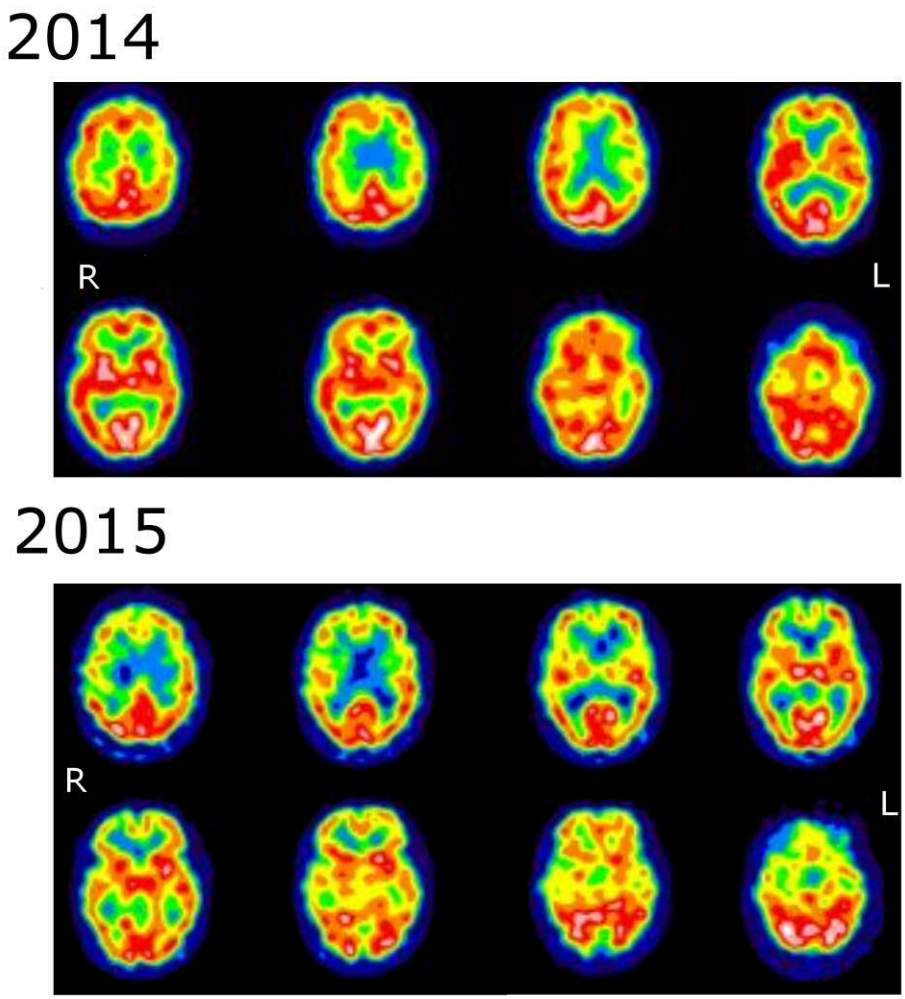

Figure 4.1. SPECT scans for NB. Axial slices for NB taken in July 2014 and August 2015. R=Right, L=Left

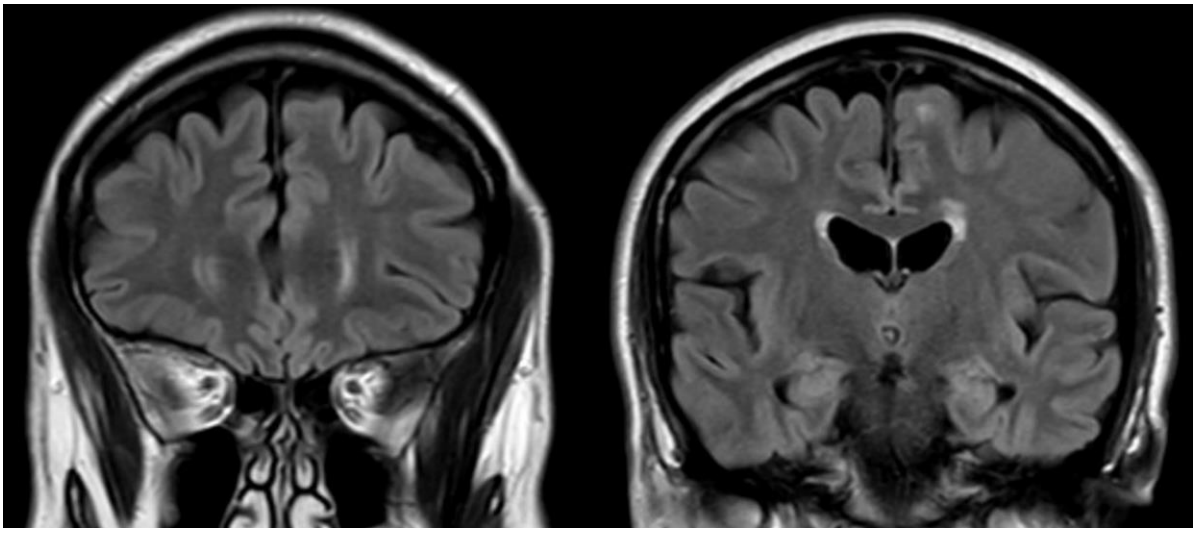

Figure 4. 2. Example MRI slices of NB from 2015 showing the frontal lobe (Left) **and temporal lobes** (Right)

4.2.1.2 Neuropsychological assessment

In the summer of 2015, NB completed clinical neuropsychological assessment. At this assessment NB's estimated IQ was 123 (verbal), putting him in the superior range at around the 93rd Percentile. He scored 23/30 on the MOCA. He exhibited, however, prominent impairment on a range of standard neuropsychological assessments. In particular, his visuo-motor speed, phonemic verbal fluency and visual analysis and construction all lay within the low average to impaired range (See Table 1). He showed particular impairment on episodic memory tasks including verbal recall, story recall and visual recall, for all of which he scored within the impaired range. On self-report he reported his memory in everyday situations to be well below his previous abilities. His performance on the Wisconsin Card Sorting Test of executive functioning was however within the normal range.

NB completed the tasks for this study early in the summer of 2017. At the time of testing, NB was aged 65. At testing NB appeared engaged and motivated to complete the tasks. No cognitive assessments were administered at the time of testing beyond those reported here.

Domain	Assessment	Performance percentile
IQ	Reading test	93
Verbal working memory	Digit Span	62
Visuomotor speed	Trails A	3
Abstract verbal reasoning	Similarities	62
Phonemic verbal fluency	FAS	16
Semantic verbal fluency	animals	31
Visual construction	Block design	10
Memory	Immediate recall	<1
	Delayed recall (retention)	38
	Logical memory	<1
Psychomotor speed	Trails B	<1

Table 4.1 The Neuropsychological Profile of NB at testing in Summer 2015

4.2.2 Healthy control participants

NB's performance was compared to a control comparison group of seven healthy individuals (HC) matched to NB on gender, educational level and age. Healthy participants were recruited via The School of Psychology Community Panel at Cardiff University.

4.2.3 Ethical Approval

Ethical approval for this study was obtained from NHS England's Health Research Authority and Cardiff University School of Psychology Research Ethics Committee. Prior to study recruitment, NB was judged by a clinician to be capable of providing informed consent. NB expressed an interest in taking part in the study following a postal invitation to participate. All study participants including NB provided written informed consent. All participants were informed that the study would involve audio recording and provided consent for their data to be included in this thesis and potential research publications. Further to this consent, NB provided additional consent for his medical records to be assessed, including access to clinical scans and previous neuropsychological assessments.

4.2.4 Experimental Tasks

All participants completed three tasks, an abbreviated version of the RMET (see below), the SST (described in the previous chapters) and the NART. An abbreviated version of the RMET was utilised due to the time constraints of testing within a clinical context and included only the emotional (and not the neutral) items, as detailed in chapter 2.

As I both recruited participants and marked their SST performance, I was not blind to disease status during marking. While trials for RMET and NART receive binary correct/incorrect responses and are open to little interpretation, scores on the SST require interpretation and as such may be sensitive to rater bias. To ensure that scores were reliable a second rater was provided with a selection of SST recordings including all those reported here but not limited to these cases. Rater 2 was blind to disease status and naive to the nature of bvFTD. To assess the degree of agreement in scores between the two raters interclass correlation coefficient estimates and their 95% confidence intervals were calculated using SPSS statistical package version 23 (SPSS Inc. Chicago, IL). A two-way random model was used with calculations assessing absolute agreement. To maximise agreement on final scoring of the SST, questions on which scores differed were considered. Discrepancies in interpretation of the marking criteria were considered and in light of this, divergent scores were re-evaluated and altered if appropriate (See results for further details).

4.2.5 Data analysis

In recent years, rigorous operational definitions of dissociations in single-case studies have been provided, together with formal statistical methods (Crawford, Garthwaite, & Gray, 2003). Specifically, “the operational definition of a “classical” dissociation incorporates a requirement that a patients’ performance on task X is significantly different from Task Y, in addition to the “standard” requirement that the patient has a deficit on Task X and is within normal limits on Task Y” (Crawford et al., 2003).

Bayesian analyses were conducted to test for differences between NB and HC performance and dissociations within NB’s performance. Since NB’s performance was compared to a matched control sample Crawford and Garthwaite (2007) Bayesian approach for the analysis of single

cases was used. This analysis method allows for relatively small control groups (<10) to be used as a comparison group (Crawford & Garthwaite, 2007). To compare task performance of NB with HC, the computer program SingleBayes (Crawford & Garthwaite, 2007) was used.

To test for dissociations in NB's performance, Crawford and Garthwaite (2007) Bayesian test for dissociation, the Bayesian Standardised Difference Test, implemented using the DissocsBayes.exe computer program was used (available online at: http://homepages.abdn.ac.uk/j.crawford/pages/dept/BayesSingleCase.htm). DissocsBayes was selected as an analysis method as it was necessary to run analyses on standardised scores as the tests being compared have different means and standard deviations, so comparison of raw scores is not meaningful.

Given the differences in the demands of the SST-M and RMET, it is feasible that any dissociation observed between the two may be due to the memory or story comprehension demands of the SST. To control for such a possibility, additional analyses were run with SST-C as a covariate. For the purposes of covariate analysis, the BSDT_Cov analysis program was used (Crawford & Garthwaite, 2007; Crawford et al., 2003; Crawford, Garthwaite, & Ryan, 2011).

Deficits were expected to be present in NB relative to HC and so one-tailed analyses are reported where appropriate. Alpha was set to $P < 0.05$ (1-tailed). Bayesian Standardized difference tests assess the probability that absolute differences for a member of the control population would be greater than that of the target, for these assessments p-value results were akin to the results of a 2-tailed frequentist test.

4.3 Results

4.3.1 Participant characteristics

HC participants reported on average 20.3 years of formal education (SD=2.6) and had an average age of 65.5 years (SD=1.4 years).

4.3.2 Inter-rater reliability

A high degree of agreement (Koo & Li, 2016) was seen between raters for the mental state scores on the SST (SST-M)(ICC=0.92, 95% CI = 0.594, 0.984). Agreement was 100% between raters for SST-M questions for NB but some discrepancies were present for HC. Following review of scoring, no score was altered by more than 1 point (out of maximum total of 16). Scores were corrected both up and down, though more HC scores were corrected down, providing a more stringent test of differences between NB and HC. Good agreement between raters was seen for the non mental state comprehension scores on the SST (SST-C), though slightly lower than that seen for SST-M, (ICC=0.821, 95% CI - -0.106, 0.967). Scoring was identical for three of the five SST-C questions and remaining differences were due to discrepancies in the interpretation of the scoring rubric. As such, no SST-C scores were altered for either NB or HC.

4.3.3 Task performance

4.3.3.1 NART

One HC (participant 6) reported having previously completed the NART and therefore their data was excluded from NART analyses due to reports of having previously practiced the words and the participant showing 100% accuracy on the test. NB's NART score (see Table 1) did not differ from HC (p=0.130) and was above an estimated 87.0% of the population (95% Bayesian Credibility interval (95% CI) = 1.0% - 39.7%).

4.3.3.2 Reading the Mind in the Eyes

NB did not differ from the HC on the RMET (p=0.382), with 61.8% of the population scoring below NB (95% CI = 32.9% - 86.2%). NB's scored of 9 (out of 12) and 6 (out of 8) for negative and positive respectively and sat less than one standard deviation away from the average performance of controls for negative (M=8.7±1.2) or positive (M=5.6±1.3) trials.

4.3.3.3 Short Story Task

NB's performance on the SST-C did not significantly differ from performance of HCs (*p*= 0.301), with an estimated 69.9% of the population falling below NB's performance (95% CI= 39.3% - 90.8%). A striking and substantial impairment was however seen on the SST-M. NB's SST-M scores significantly differed from those of the HC (*p*=0.006) with only an estimated 0.5% of the population scoring below NB (95% CI = 0.0%- 6.2%).

	NART (errors) (Max = 50)	**RMET (Max=20)**	**SST-M (Max=16)**	**SST-C (Max=10)**
NB	7	15	1	9
HC				
1	10	14	7	10
2	13	12	5	6
3	16	14	9	8
4	23	14	10	7
5	8	18	6	6
6	-	12	10	10
7	14	16	8	10
Mean (SD)	14.0 (5.3)	14.3 (2.1)	8.1 (1.9)	7.9 (2.0)

Table 4.2. Scores for NB and HC on each of the study tasks

4.3.4 Testing for Dissociations

Z-scores were computed for NB's performance for each of the two primary outcomes of interest, the RMET and SST-M. Standardised scores for NB on the RMET showed his performance to be close to the mean (z = 0.333), while for the SST-M NB's score was substantially below normal performance, sitting more than three standard deviations below the mean (z=-3.737). The discrepancy between these two scores was significantly greater than that which would be expected in the general healthy population (p=0.046), indeed only 2.3% (95% CI = 0.0%-16.2%) of the population would be expected to show a larger discrepancy between scores. This finding is consistent with the Bayesian criteria for a "classical" dissociation (Crawford et al., 2003)

Additional analysis was carried out to determine whether a dissociation was present for NB's scores on the two components of the SST. NB's Z-score for the SST-C was 0.586, again, indicating a score well within the normal range of population scores. As described above, this compares to a z-score of -3.831 for the SST-M. The discrepancy between these two scores was again greater than that which would be expected in the general healthy population (p=0.006), indeed only 0.3% (95% Interval = 0.0%- 2.3%) of the population would be expected to show a greater discrepancy between these scores. This again provides evidence for NB showing a classical dissociation between mental state understanding and non mental state comprehension on the SST.

4.3.5 Controlling for SST-C

The presence of a dissociation in performance between RMET and SST-M performance was assessed when accounting for individual differences in performance on the SST-C. Z-scores for the tasks of interest were as reported above. After accounting for performance on SST-C, NB's z-score for the RMET (z=0.480) remained within normal bounds. His performance on SST-M, however, (z=-4.635) was even more discrepant from the performance expected for an individual from the healthy population. Evidence was sufficiently strong to reject the null hypothesis that the case belongs to the normal population (p=0.03). The effect size (Z-DCCC (Crawford, Garthwaite, & Porter, 2010)) for the difference between NB's performance and that of the HC was 3.473 (95% Bayes CI = 0.704, 5.785). An estimated 3.0% of the population would

be expected to have scores more discrepant than that of NB (95% Bayes CI = 0.0%-24.1%). This further confirms the presence of a classical dissociation in NB's performance between mental state reasoning (SST-M) and mental state decoding (RMET).

4.3.6 Qualitative consideration of performance

NB's performance was notable in his ability to provide coherent and detailed responses to SST-C questions but notable difficulty and delay in responding to SST-M questions. In contrast to SST-C items, questions involving mental state and emotion (e.g. 'Why does Nick say to Marjorie "you know everything") were initially responded to with a long pause followed by NB stating that he could not recall (a response rarely given by HC). When encouraged, NB frequently stated that he didn't know and tended to give relatively unelaborate responses, for example, in response to the question "Why is Nick afraid to look at Marjorie" NB's response, after initially stating that he did not recall was "Well I think they'd fallen out and he didn't want to uhh see uhh, have eye contact, I don't know". In fact showing a reasonable comprehension of the events of the story but limited comprehension of the intentions of the characters.

4.4 Discussion

Assessments of mental state inference based on narrative fiction have promise for the selective assessment of mentalising both for the study of neurocognitive networks underlying cognitive empathic functioning and as assessments that may have the potential to assist in the early detection of bvFTD. As an initial test of this idea, here, I presented the case of a high functioning individual (NB) with a clinical diagnosis of probable bvFTD who showed a striking and selective impairment in explicit mental state reasoning on a novel mentalising task, the SST. This substantial impairment is here reported in the context of intact performance on a control comprehension assessment, based on the same story reading task as the mental state reasoning assessment, and, notably, normal performance on emotional items from the RMET. NB's task performance was consistent with Bayesian criteria for showing a dissociation between these tasks.

An increasing body of evidence points to pervasive deficits in bvFTD in the ability to mentalise and consider the thoughts, beliefs, desires, intentions and perspectives of others (Bora et al.,

2015). Yet, many existing tasks show considerable ceiling effects and may be insufficiently challenging to detect changes in the ability to mentalise in relatively high functioning individuals, such as those in the early stages of bvFTD. In contrast, the SST is sensitive to variation in ToM ability with a relatively normal range, and thus can detect robust brain-behaviour relations in healthy individuals (see previous chapter). This is likely due to the requirement of participants to understand a sophisticated, subtle and dynamically evolving interpersonal narrative and provide free responses to open questions rather than respond to prescriptive forced choice responses. The work presented in this chapter is evidence for a profound inability to reason about the mental states of characters in a high functioning individual with bvFTD. This suggests that the SST may be a very sensitive, ecologically valid, cognitive neuropsychological assessment of impaired mentalising ability in even high functioning individuals with bvFTD which suggesting that this task may have clinical utility for the detection of bvFTD.

Here, NB's deficit on the SST appeared specific to mental state understanding, with his comprehension of the non mental state aspects of the story remaining unaffected. The profound impairment in mentalising seen here is consistent with the known pathology of bvFTD. Across pathological subgroups of the disease, co-localised grey matter and white matter degeneration is seen in regions corresponding to the posited mentalising network, including dorsal and vmPFC and CB (Mahoney et al., 2014; Perry et al., 2017), consistent with the network neurodegeneration account of bvFTD (Seeley et al., 2009). Interestingly, given the general high level of functioning of NB, a recent study (Cash et al., 2018) found GM reductions in frontal regions associated with the mentalising network, even in presymptomatic mutation carriers. My findings thus suggest that the SST might be a suitable probe of subtle mentalising impairments thain the early stages of bvFTD.

The observed relative sparing of facial emotion decoding in an individual with bvFTD is somewhat surprising. Impaired facial emotion perception is fairly frequently reported in FTD (Bora, Velakoulis, & Walterfang, 2016; Fernandez-Duque & Black, 2005; Kumfor et al., 2011), indeed altered facial emotion perception has been seen across a range of tasks including the 'Ekman faces' (Janine Diehl-Schmid et al., 2007; Keane et al., 2002), emotional hexagram (Buhl et al., 2013), TASIT (Kipps et al., 2009; Shany-Ur et al., 2012) and, the RMET (Bora et al., 2015; Gregory et al., 2002; Torralva et al., 2007; Torralva et al., 2009). One important consideration

regarding the discrepancy between this study and previous work is that here I used a shortened version of the RMET, comprising only emotional and not cognitive RMET items. Given that an impairment of cognitive empathic functioning is present in FTD it is possible that a deficit on the RMET could be driven, in some cases, by selective impairment on the cognitive state items (Harkness et al., 2005). This would not however explain previous reports of substantial deficits on face emotion expression decoding tasks such as the Ekman 60 (Janine Diehl-Schmid et al., 2007; Keane et al., 2002), the emotional hexagon (Buhl et al., 2013), and the emotion evaluation component of the TASIT (Downey et al., 2015; Kipps et al., 2009; Shany-Ur et al., 2012) in bvFTD. None of which involve cognitive state expressions. Nevertheless, heterogeneous performances on facial emotion perception tasks at an individual level have been reported in bvFTD (Cerami et al., 2015; Fernandez-Duque & Black, 2005; Keane et al., 2002). At least one case has also been reported (Lough et al., 2001) of an individual with bvFTD who showed spared RMET performance but impaired performance on second-order belief and faux pas tasks of mental state reasoning (although standardised difference tests were not conducted in that study).

The dissociation between cognitive components of affective and cognitive empathic functioning shown here is consistent with the proposals outlined in the introduction that these skills are underpinned by distinct neurocognitive systems (e.g. Blair, 2005; Tager-Flusberg and Sullivan, 2000). Cognitively, such a dissociation is evident in a range of clinical groups including alcoholism (Maurage et al., 2011), anorexia (Russell, Schmidt, Doherty, Young, & Tchanturia, 2009), borderline personality disorder (Harari et al., 2010), epilepsy (Jiang et al., 2014), Schizophrenia (Bonfils, Lysaker, Minor, & Salyers, 2017; Michaels et al., 2014; Shamay-Tsoory & Aharon-Peretz, 2007) and Huntington's disease (Maurage et al., 2016). Impairment in cognitive empathy, in the face of apparent preservation of affective empathy, is seen in a number of clinical groups (Harari et al., 2010; Jiang et al., 2014; Maurage et al., 2016; Rogers et al., 2007), and double disassociation between these abilities is apparent thanks to impairment in affective empathy, in the face of preservation of cognitive empathy, in alcoholism and Schizophrenia (Maurage et al., 2011; Shamay-Tsoory & Aharon-Peretz, 2007).

The findings of this chapter suggest that there may well be a neural basis to the dissociation of cognitive and perceptual empathy. These dissociations cannot however rule out the possibility that two tasks might utilise the same social cognitive network, but in a graded fashion (Shallice,

1988). This concern is however mitigated by the converging findings of a correlational double dissociation between the white matter microstructural correlates of RMET and SST-M, as detailed in the chapter 3. Existing lesion work additionally supports the presence of the dissociation of these two neurocognitive components of empathy (Herbet, Lafargue, Bonnetblanc, Moritz-Gasser, & Duffau, 2013; Shamay-Tsoory & Aharon-Peretz, 2007) and, consistent with the findings of the previous chapters, has shown the involvement of medial frontal structures in cognitive empathy and lateral regions in affective empathy (Shamay-Tsoory et al., 2009). Work using voxel based morphometry in SD has further shown that the volume of medial frontal regions, including vmPFC and ACC, showed a correlation with performance on false belief tasks, while performance on the same 20 item RMET task used here was related to volume of the amygdala and surrounding ATL (Bejanin et al., 2017).

The results presented here show the value of investigating single cases. As highlighted, single cases allow the consideration of individual variability in functioning, which is lost in group studies. A risk of single case studies is however that conclusions may be made based on unusual or uncharacteristic cases. A limitation of the current work is that NB shows a number of features that are not entirely consistent with the classic presentation of a case of bvFTD, such as visuospatial changes and apparent insight into aspects of his condition. As highlighted in the introduction, molecular and neuro-pathology in bvFTD is highly variable (Beck et al., 2008; Hsiung et al., 2012; Rohrer et al., 2011) and as such this case may represent an unusual case, such as an individual with a C9ORF72 mutation who sometimes present with unusual clinical characteristics. Yet it is always a risk of case studies that cases may not be truly representative of the disease in question. To further clarify the nature of this case genetic testing would be of benefit, of particular relevance here, is evidence that while all pathological variants of bvFTD show similar alteration in medial frontal structures, carriers of the MAPT mutation appear to have greater involvement of ATL and UF relative to other variants (Cash et al., 2018; Mahoney et al., 2014). Unfortunately, genetic testing was unavailable for NB and as such, a consideration of the potential impact of genetics is not possible here. Future large-scale studies are needed to address the relationship between molecular, neural network and social cognitive pathology in FTD. While it may not be feasible in all cases, long term follow-up of single cases would represent a gold-standard to ideally allow for a post-mortum verification of disease pathology to ensure that cases are indeed identified accurately.

Despite the novel contribution of this work and its consistency with the previous chapters the lack of quantitative GM and WM imaging prevents me from making claims about the link between specific network neurodegeneration and cognitive functioning reported here. Nevertheless, the single-case approach is the appropriate methodology for drawing inferences about the functional architecture of social cognitive processes in research involving brain-damaged patients (Caramazza & McCloskey, 1988), especially in the context of anatomical heterogeneity across cases (Shallice, 2015). It does however seem highly plausible, that dysfunction in medio-frontal grey and white matter may have a substantial role in the functional impairment reported here. Unfortunately, this study does not provide direct evidence of the nature of the neurodegeneration that underlies the impaired cognitive functioning seen here. The limited specificity of clinical imaging present in this case allows for limited consideration of structural alteration, especially in relation to white matter. A further limitation of this case was that structural imaging was not carried out at the time of cognitive testing and as such an accurate characterisation of the brain structural abnormality at the time of cognitive testing was not available. Future work should extend this study by carrying out both detailed neuropsychological assessment of individuals with bvFTD using the tasks here and research-quality scanning, including functional, volumetric and DWI, at both the individual and group levels. Such work would allow for a detailed examination of the relationship between network level neurodegeneration (including change in specific white matter pathways including CB and UF) and functional performance on tasks, such as the SST, assessing specific cognitive components of social functioning, including those sensitive to cognitive and perceptual components of empathic functioning.

A limitation of this work is the delay between clinical neuropsychological assessment and experimental assessment. Due to the delay between these assessments it is not possible here to accurately determine NB's current disease staging at the time of testing, nor is it possible to consider his performance on clinical neurocognitive assessments in relation to his performance on the experimental assessments. As it is not feasible to compare between clinical and experimental assessments we are not able to directly consider NB's performance on clinical assessments executive functions in relation to his experimental performance and as such the lack of detailed assessment of executive function in the experimental protocol limits our ability to make conclusions regarding the impact that executive abilities may have had on task performance. As discussed in chapter 3, the relationship between mentalising and executive

function is a topic of ongoing controversy (Apperly, Samson, & Humphreys, 2009). However, a recent paper (Bertoux, O'Callaghan, Dubois, & Hornberger, 2016) used a statistical clustering approach to show that mentalising, as measured using the faux pas test, was independent of executive functioning in individuals with bvFTD. Consistent with a number of previous findings (Gregory et al., 2002; Lough et al., 2001; Lough et al., 2006). That said, these tasks have tended not to involve text-based mentalising and as such, it cannot be ruled out that executive function may have a role here. While this seems unlikely, given that the demands of answering the comprehension component of the task are in many ways not dissimilar to those of the mental state component, and no deficit was seen here, this will be important to examine in future studies to confirm independence of these functions.

A clear next step from this work, based on the findings of chapters 2 and 3, is to explore the relationship between performance on assessments of cognitive and perceptual components of empathy and microstructural properties of white matter tracts in individuals with bvFTD. An inevitable issue of correlational work is the absence of any direct evidence that the two processes are directly related to each other. As such, though compelling, the evidence from the previous chapters does not provide conclusive evidence that the white matter metrics discussed directly relate to functional performance. To make such direct links and to make claims regarding the necessity of specific structures for functioning, evidence of impairment in the function due to alteration to the structure is necessary. It is for this reason that the consideration of neural alteration in FTD and its relationship to performance on these tasks may be of particular value as such work would provide more direct evidence of a causal relationship between white matter microstructure and cognitive functioning. If variability was indeed seen across these individuals it would give further support the disassociation shown here and may provide further evidence for the key importance of the UF and CB in facial emotion processing and mentalising respectively.

The task used here has a number of strengths over previous mentalising assessments used in bvFTD in particular thanks to its naturalism. Yet, while the task used here is more naturalistic than many previous assessments of mentalising, the SST still requires explicit rather than spontaneously deployed mindreading and it is unclear whether our processing of fictional social agents is truly identical to the processing of actual social agents (Oatley, 2016). A further exploration of naturally occurring social behaviour is presented in chapter 5.

In this chapter, I presented a single case study of a high functioning individual with a clinical diagnosis of probable bvFTD. I found strong evidence for a novel selective impairment in the ability to understand the mental states of characters in a fictional interpersonal literary narrative. This impairment was seen to be cognitively dissociable from comprehension of the non mentalistic aspects of the narrative and the ability to decode facial emotion expressions which were seen to be intact. From a clinical perspective, my findings suggest that text-based assessments of mentalising may have the potential to be a sensitive marker of the presence of bvFTD early on in disease course. In addition, they are consistent with the proposed neural network level dissociation between cognitive and perceptual components of empathic functioning and suggest that bvFTD may be an important clinical paradigm for probing the network neuroscience of empathic functioning.

5

A qualitative exploration of social and empathic behavioural change in FTD from the perspective of family members

5.1 Introduction

Social cognitive functioning is highly complex, dynamic and intrinsically interpersonal. Given this, social cognition is best explored within its natural social context (Zaki & Ochsner, 2009). Yet, in FTD, the everyday social behaviours of individuals with FTD, and thus the impact of environmental and contextual influences on social behaviours, remain largely unexplored (Ibanez & Manes, 2012). If we are to fully understand the nature of the social cognitive impairment in FTD we must thus first appreciate and study the real world behaviour of individuals with FTD and examine the relationship context in which their social and empathic changes occur. Qualitative methods provide an avenue for such work and the study of complex, dyadic, contextual behaviours (Madill & Gough, 2008). Such research may provide critical information about the nature of behavioural changes, such as their impact on others and their underlying cognitive cause, which may not be accessible using other methods.

As previously discussed (See introduction and previous chapters), most research into social cognitive and empathic functioning in FTD has utilised controlled experimental designs. Yet such experimental studies provide limited characterisation of the interactional nature of social behaviours. Experiments are conducted in artificial, unfamiliar and challenging environments and rarely involve evaluating social behaviour in familiar environments with familiar interaction partners. These aspects of experiments will influence an individual's performance and result in responses that may differ from their everyday behaviour. This means that not only do these studies provide no information on how identified impairments on cognitive tests may manifest in changes to everyday behaviour, behavioural changes experienced by families and symptoms which lead a diagnosis, there is a "validity gap" between laboratory and naturalistic assessments of social cognitive ability. Contextually-relevant research methods describing day to day, naturally

occurring behaviours are thus necessary to expand our understanding of social cognitive breakdown in FTD.

Descriptions of everyday behaviour in FTD may elucidate how and why behavioural changes affect families and undermine close relationships. Caring for a partner with FTD can take a substantial toll on marital satisfaction (Ascher et al., 2010) and lead to significant burden (Hsieh et al., 2013). Social and empathic changes may have a key role in this as empathic change has been seen to be destructive to the marital bond (Ascher et al., 2010; Nunnemann, Kurz, Leucht, & Diehl-Schmid, 2012), lead to burden (Hsieh et al., 2013), and depression (Diehl-Schmid et al., 2013; Brown et al. 2017). Indeed the level of burden reported by family members of individuals with amyotrophic lateral sclerosis has been seen to be more closely related to their behavioural symptoms than their physical disability (Lillo, Mioshi, & Hodges, 2012). Loss of emotional attachment due to behavioural symptoms may be one potential cause of this (Massimo, Evans, & Benner, 2013). Though such work indicates that behavioural change may lead to challenges for families, further characterisation of the nature of social behavioural and empathic changes may help us to develop a better understanding of how these behaviours lead to negative outcomes such as burden and depression.

Qualitative methods are an established approach to obtaining reports of behavioural change from family members in clinical research and for investigating dynamic and interpersonal behaviour (Madill & Gough, 2008). Though qualitative studies are not abundant within the early onset dementia literature, they have been used to investigate the impact of providing care for individuals with young onset dementia (Cabote, Bramble, & McCann, 2015) and FTD specifically (Kindell, Sage, Wilkinson, & Keady, 2014; Kumamoto et al., 2004; Massimo et al., 2013; Oyebode, Bradley, & Allen, 2013; Spreadbury & Kipps, 2017). Such work has shown that social changes and changes to relationship dynamics are particularly challenging to family members (Massimo et al., 2013; Oyebode et al., 2013). Research to date has however tended to give little consideration to the *nature* of behavioural changes themselves, yet in the traumatic brain injury and ASD literatures, qualitative methods have shown value when used to study social behaviour and investigate the impact specifically of social and personality change on families and relationships (Bodley-Scott & Riley, 2015; Godwin, Chappell, & Kreutzer, 2014; Lefebvre, Cloutier, & Josee Levert, 2008) and quality of life (Kratz, Sander, Brickell, Lange, & Carlozzi, 2017).

There are few studies currently within the literature that have explored the manifestation of the behavioural symptoms of FTD in a social or relationship context. Those studies that have, have been primarily observational and have considered both social (Barsuglia, Nedjat-Haiem, et al., 2014; Ghosh, Dutt, Bhargava, & Snowden, 2013; Mendez et al., 2014; Rankin et al., 2008) and non-social behaviours (Ghosh et al., 2012). Indeed many of these studies still give a relatively limited description of the nature of behavioural symptoms as they utilise restrictive methods for symptom reporting. Two such studies that involved the observation of the behaviour of indivdiuals with FTD in clinic (Rankin et al., 2008) and during a meal at home (Mendez et al., 2014), however both reported on behaviour through the lens of prescribed observational behaviour rating scales, the Interpersonal Measure of Psychopathy (Rankin et al., 2008) and the Social Observation Inventory (Mendez et al., 2014). One of these studies did give additional detail and discussed the notable absence of "your" statements within mealtime interactions (Mendez et al., 2014). While analysis of this observation was given, suggesting that this behaviour may indicate egocentrism and a failure to consider the mental perspective or needs of others, little further discussion of the nature of the observed behaviours was given in either study.

Barsuglia et al., (2014) reported one of the few studies that has provided a richly detailed qualitative analysis of social behaviour in FTD. In this work the researchers made detailed observations of individuals with FTD during multiple research visits, together with up to three visits to the participant during their daily life in locations such as their home, coffee shops, parks or restaurants. Each observation lasted for up to 4 hours. The notes accumulated from these observations were qualitatively analysed with descriptions of behaviours being coded for behavioural themes using thematic analysis (Braun & Clarke, 2006). In this work three themes were identified: *diminished relational interest and initiation of social interaction*; *lack of social synchrony*; and *poor awareness of or adherence to social norms.* Two of these themes described a tendency for reduced social engagement and social connection, though both focused primarily on verbal interaction. Ignoring the questions of others, a failing to engage in conversation, interrupting conversation, giving short or blunt responses and asking inappropriate and intrusive questions were highlighted. The third theme highlighted behaviours that did not fit within social norms, such as poor manners, inappropriate comments, inappropriate jokes and over-sharing personal information. These reports were more descriptive than analytical but captured aspects of the dynamic and interactional nature of social behaviour. In the work, empathic concern was

directly discussed as a sub-theme within the theme of lack of social synchrony. Altered empathic concern was described as a lack of response to distress of others with an example is given of a participant failing to comfort his crying wife. Though this work represents a major step forward and is one of the most comprehensive descriptions of altered behaviour in FTD to date, empathic behaviour in particular was considered in only limited depth and no consideration was given to the potential cognitive alterations that may underlie the observed alterations in empathy.

Previous observational work has captured aspects of the dyadic nature of social behaviour, describing interactions of individuals with FTD with both researchers (Barsuglia, Nedjat-Haiem, et al., 2014; Rankin et al., 2008) and family members (Barsuglia, Nedjat-Haiem, et al., 2014; Mendez et al., 2014), however such work has failed to include the perspective and experience of family members, and as such it remains limited. The relational aspects of social behaviour picked up by such work are fundamental to social functioning, but which are typically lacking in most experimental assessments of social and empathic behaviour. Barsuglia et al (2014) in particular discusses the *responsiveness* of individuals with FTD to others, a component of behaviour critical to relationship quality and duration (Reis & Gable, 2015). Yet, while such work captures aspects of behaviour, the dyadic nature of social behaviour means that individuals involved in interactions have insight into their nature beyond what may be apparent to a naïve observer. This is particularly the case for family member interactions with individuals with FTD, as family members have rich and extensive knowledge of their relative. This includes experience from prior to the development of FTD and thus family members are able to comment on what behaviours represent behavioural change rather than behavioural abnormality. Such rich relationship knowledge may allow family members to detect and interpret behavioural manifestations of FTD that would not be obvious to less well-acquainted observers and separate behavioural quirks from behavioural changes. The existing literature thus misses a valuable source of information on social behavioural change by not including the knowledge and experience of family members.

One way to examine questions regarding everyday social behaviour in FTD is to obtain family members' accounts. Existing work using family member reports has tended to utilise prescriptive questionnaires, which give only limited detail or consideration of the impact of social context on behaviour. Questionnaires such as the Interpersonal Reactivity Index (IRI) (Eslinger et al., 2011; Fernandez-Duque et al., 2010; Oliver et al., 2015; Eslinger et al., 2011; Fernandez-Duque et al., 2010; Oliver et al., 2015) and the Cambridge Behavioural Inventory (CBI) (Mioshi et al., 2013) are

typically used. Such research has highlighted the presence of changes in mentalising, interpersonal warmth and empathic concern in FTD (Eslinger et al., 2011; Hsieh et al., 2013; Rankin et al., 2005). While such work has been described as characterising interpersonal deficits in FTD (Eslinger et al., 2011), it provides only limited description of everyday behavioural alterations. Calls have been made for observational and naturalistic investigation of real time dynamic social interactions (Lough et al., 2006) and perspective taking abilities (Hsieh et al., 2013) to strengthen the results of such work. There remains, however, a dearth of detailed family member reports of social behavioural change within the literature.

Reports from family members allow for comments on behaviours to be made from a wide timespan and across a range of situations. The existing body of observational work on social behaviour in FTD is limited in that it covers a relatively restricted portion of social contexts. Existing work tends to disproportionately describe behaviour in a clinical context and in interactions with researchers (Barsuglia, Nedjat-Haiem, et al., 2014; Ghosh et al., 2013; Rankin et al., 2008). Such situations are not representative of individuals' day-to-day surroundings as they can be novel, stressful and study participants may be aware of being observed or under scrutiny. Thus it is hard to claim that behaviours observed in these situations are valid indicators of the individuals' behaviours outside of the clinic. Though work has been carried out outside this context reports that describe behaviour outside of clinical settings (Barsuglia, Kaiser, et al., 2014; Mendez et al., 2014) still fail to cover even a small proportion of daily life and thus many behavioural changes that may be characteristic of FTD or have prominence for families won't be observed. Family (retrospective) reports may be of value to overcome this and can also capture early behavioural changes, which inevitably take place before families will have obtained a diagnosis and thus can be enrolled in quantitative or observational research.

In this chapter, I will present a study in which I utilised qualitative analyses, based on family member narratives of behavioural change, to explore the dynamic and interactional nature of social and empathic behavioural change in FTD. Descriptions were collected of natural and contextually bound changes in everyday social interactions from longstanding and meaningful interpersonal relationships. These descriptions were collected from the perspective of family members who know the individual with FTD well and regularly interact with them. The interpersonal, interactional components of behaviours were of particular interest, being difficult to assess using standard experimental methods. I envisaged that collecting such descriptions and

considering the commonalities amongst descriptions would add another dimension to our understanding of the breakdown of social cognitive and empathic functioning in FTD.

Semi-structured interviews were used as they are neither prescriptive nor hypothesis led and can be used to obtain detailed descriptions of behaviours. The semi-structured nature of the interviews allowed for family members to play an active role in determining what was present within the data, ensuring that social behaviours that were most prominent for the interviewees were discussed. This is important, as such behaviours could potentially be discussed in initial clinical visits and thus may be of diagnostic utility. Methodologically, the open and non-prescriptive approach made this work suited to grounded theory, an inductive approach to qualitative data interpretation. Grounded theory is a flexible set of guidelines for the collection and analysis of qualitative data in which trends within the data emerge through iterative coding and consideration of themes within the data (Charmaz, 1990). The grounded theory method aims to produce an inductively driven theory of psychological processes grounded in the data (typically transcripts of interview data) from which it was derived (Charmaz, 2006). The method is particularly suitable here as it allows not only for a systematic approach to data analysis and the provision of rich and detailed data, but also provides a basis from which to conceptualise potential underlying causes for behavioural change, a key goal of my work (Charmaz, 2006; Hussein, Hirst, Slaywers, & Osuji, 2014). Grounded theory is a method for identifying emergent themes from qualitative work (Charmaz, 1990, 2006), it has been used to study social processes such as affection and emotional responsiveness (Bodley-Scott & Riley, 2015) and is valuable in underexplored domains as it is inductive and hypothesis forming. This suggests that there may be value in applying this method to the study of social and emotional change in FTD.

Family members rather than individuals with FTD were interviewed because, in addition to providing a novel perspective on the wider social ramifications of cognitive and behaviour change in FTD, this approach sidesteps some of the problems of reliability inherent to first-person reports. Further to this, a profound lack of self-insight is seen in FTD (Hornberger et al., 2014; O'Keeffe et al., 2007), meaning that those with FTD are likely to be poor informants on their own symptoms. Consistent with this, in quantitative studies, a significant discrepancy is seen between reports of empathic behaviour given by individuals with bvFTD and their family members (Hsieh et al., 2013; Rankin et al., 2005). Family members report being acutely aware of behavioural, personality and communicational change (Oyebode et al., 2013)) and changes in social abilities substantially

impact on their lives (Brioschi Guevara et al., 2015). Social behavioural and cognitive change may thus be more obvious for interaction partners than the individual themselves. Speaking to family members may thus help us to capture the sociality of social cognition often absent from social cognition research and ensures more reliable reports of behaviour than may be obtained from affected individuals themselves.

5.2 Methods

5.2.1 Participants and recruitment

Recruitment took place in collaboration with the FTD UK Caregiver Support Group. Study information was provided within the group's newsletter and at the group's annual meeting. Eleven individuals expressed an interest in taking part, seven relatives of individuals with bvFTD, three relatives of an individual with SD and one relative of an individual with the logopenic variant of primary progressive aphasia. Only relatives of individuals who had previously received a diagnosis of a variant of FTLD and who reported profound impairments in social behaviour were included in this work. Family members of individuals with a diagnosis of logopenic dementia were therefore excluded due to the presence of profound language impairment and likely involvement of Alzheimer pathology (Harris et al., 2013). The data for this study thus consisted of ten interviews with a total interview time of 22hr 30min. The shortest interview being 1hr 15 minutes and the longest lasting 3hr. Eight interviews took place in interviewees' homes and two took place over the telephone. All individuals interested in taking part were included irrespective of relationship to the individual with FTD, as such, spouses made up the majority of participants but children and ex-partners were also included. Basic demographics of interviewees are provided in Table 1. Recruitment continued for the study until *saturation* was reached (Charmaz, 2006), defined as the point when no additional themes emerged from new interviews.

Pseudonym	Age	Gender	Relationship	Relationship duration (Yrs)	Diagnosis	Estimated Disease Duration (Yrs)
Steven	Late 50s	M	Husband	~30	bvFTD	~10
Stephanie	Early 30s	F	Daughter	~30	SD	3.5
Elaine	Late 60s	F	Wife	~30	bvFTD	21
John	Mid 60s	M	Husband	50+	bvFTD	7
Rebecca	Early 70	F	Wife	50+	bvFTD	11
Samantha	Late 60s	F	Widow	40+	bvFTD	7 (Deceased)
Sandra	Mid 60s	F	Ex-partner	30+	bvFTD	4
Margaret	Late 60s	F	Wife	~50	bvFTD	8
Nigel	Early 70s	M	Husband	40+	SD	3.5
Thomas	Mid 30s	M	Son	~30	SD	3.5

Table 5.1. Basic demographic information of study participants. Yrs=Years

5.2.2 Ethics

Cardiff University School of Psychology Research Ethics Committee approved this study. Written informed consent was obtained from all participants prior to data collection, as was consent for interviews to be audio recorded. It was made clear to all participants that they were free to include or exclude any topic of discussion and that interviews would be transcribed with direct but anonymised quotations being included in this and any publications arising from this thesis. During transcription all names of people and places were changed to anonymise the data.

5.2.3 Data collection

Interviews were semi-structured and focused on exploring the interviewee's experiences of social behavioural changes and their impact following the onset of FTD. Interviewees were explicitly told that the purpose of the interview was to explore their experience of changes in social interaction and empathy. These terms, however, were not further defined and interviewees were explicitly told that they were free to discuss *any* topics that they felt were relevant or of importance. Interviews began by asking for a brief background description of the interviewee's relationship with their relative, how they know each other and what their relative was like prior to the onset of FTD. From relatively early on in the discussion the vast majority of topics of conversation were

introduced by interviewees. As interviewer, I primarily directed the conversation by asking for clarification or further elaboration on points of interest. Generally, questions were structured such that the interview first focused on initial symptoms; the process of seeking and receiving a diagnosis; and then moving to a discussion of more recent symptoms. At times, I noted topics that were raised that seemed of potential relevance to social behaviour and if these had not been explored in detail I later asked for interviewees to go back to these points to discuss them in more depth.

In line with the principles of grounded theory, interviews were influenced by ongoing analysis (Charmaz, 1990, 2006). These were based on an open-ended coding of detailed interview data followed by an iterative process of re-coding and identification of emergent themes until a saturation point was reached whereby no additional themes emerged from new data. Based on the constant comparative method of grounded theory, data collection progressed in parallel with analysis, and findings from the ongoing transcription and coding directed the topics that were explored in greater detail during subsequent interviews. Detailed field notes were kept of salient points raised in each interview and these informed the codes used and themes highlighted during analysis.

5.2.4 Data coding and analysis

Interviews were transcribed using Express Scribe Transcription software (NCH Software) and during transcription notes were made on prominent themes. Following transcription, full transcripts were reviewed line-by-line and coded for emergent themes using NVivo (QRS International's NVivo 11 Software). Codes comprised of themes within the data such as: 'wandering', 'anger', 'altered eating' etc. Transcripts were read and reviewed multiple times. Following initial coding, relationships between codes were considered and similar codes were conflated while codes felt to be insufficiently specific were split. Following changes to codes transcripts were reviewed and if necessary sections were re-coded. Once all transcripts were coded the resulting codes were considered in relation to one another and grouped to identify overall themes, informed by field notes and transcription notes or 'memos' (Charmaz, 2006).

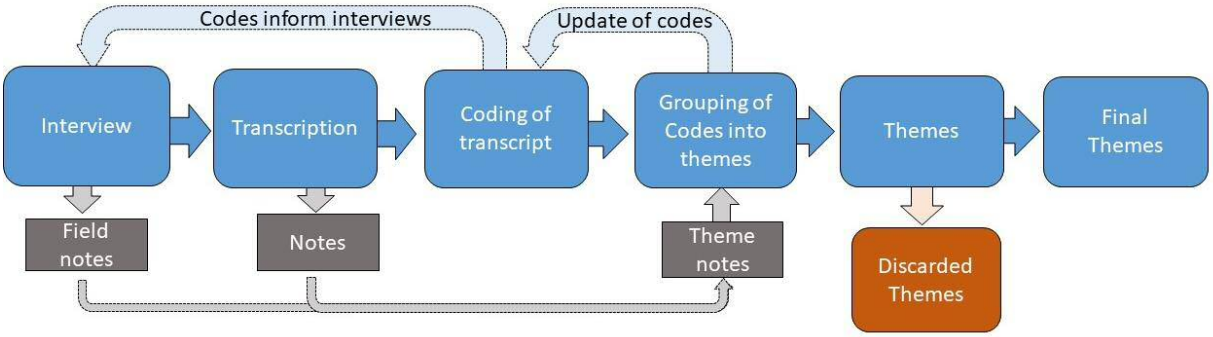

Figure 5.1. Analysis flow chart

5.2.5 Theme selection

In the development of themes, some identified themes and codes were discounted from further analysis. Firstly codes were discarded that fitted closely with domains of behavioural change identified within diagnostic criteria for bvFTD (Neary et al., 1998; Rabinovici & Miller, 2010). Such codes were; *stereotyped behaviours, apathy, and development of a sweet tooth*. These were excluded because they were not specifically social and lacked novelty. Themes were reviewed and selected for their prominence within the data. Codes that either lacked detail within single reports or lacked corroboration across reports were discarded. This was because detail is vital to allow for interpretation, and because corroboration is critical to ensure validity of themes (Charmaz, 2006). Examples of themes lacking detail or corroboration were; *prominent sexual changes*, *increased co-cooperativeness, maintained social graces with strangers and lack of interest in grandchildren*. Within the codes lacking sufficient detail or corroboration, three themes were noted to have direct relevance to the cognitive domains explored in previous chapters, these were; c*hange in interest in stories and drama*, *change in emotion expression or occurrence, and difficulty recognising people*. Of the remaining themes, those that were not specifically social were discarded due to the specific aims of this research project. Several interesting themes were therefore not explored, such as; g*ift giving, increased openness, responses to death and response to discussion of divorce*. These themes justify additional exploration and consideration in future work.

5.3 Findings

An intentionally sparse interpretation of the data, particularly in relation to existing literature, will be presented in this section. This will be given in the discussion. This is to allow for a rich qualitative description of the data, independent of imposed theoretical interpretation.

Three major themes emerged from this work that were deemed to be novel, prominent within the data and social in nature. These were; Disengagement during conflict, Sense of Humour, and Apparent Deception (see Figure 5.2).

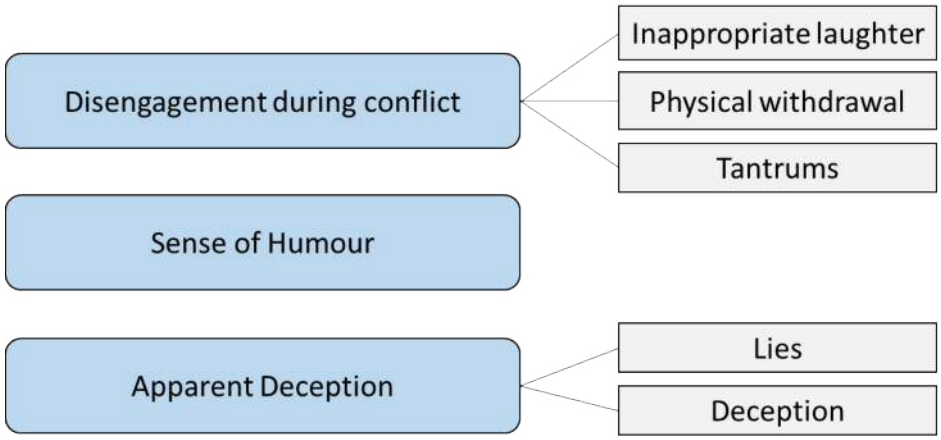

Figure 5.2 Key themes and sub-themes

5.3.1 Disengagement during conflict

Substantial changes were reported in the way interviewee's relatives engaged in or responded to conflicts or verbal disputes. These were reported as some of the earliest apparent changes that the interviewee could recall. Changes to engagement during conflict caused notable distress to interviewees and were reported to have detrimentally impacted on interviewees' relationship with their relative. Three broad categories of responses to conflict were identified: *Inappropriate laughter, Physical withdrawal and Tantrums*.

5.3.1.1 Inappropriate Laughter

Inappropriate laughter was prominent in the descriptions given by "Steven". Steven worked in finance and business, He had been married to his wife for over 20 years when he first noted a change in her behaviour, notably a change in her response to disagreement. Steven's description of the first change that he noted, encapsulates aspects of the changes in disagreement described by other interviewees:

Steven: *I started to notice some, some fairly strange behaviour or uncharacteristic behaviour I suppose, for my 50th [birthday]. I was sort of, sort of expecting a party to be organised. You don't like to ask because these things are supposed to be secret, but in fact, absolutely nothing happened. I do recall that we had well, not exactly a row about it, but I expressed my surprise that nothing had happened and I think two things stuck in my mind. The first being that she hadn't really done anything about it and secondly the fact that when I did challenge her about it there seemed to be a lack of understanding as to why I should be upset about it. I mean she said a few things, sort of relatively platitudinous things, but didn't really seem to grasp that I would be upset by the fact that a major birthday hadn't been celebrated and I think that that was the first of a number of occasions where I got, I think in any healthy relationship there are disagreements and rows and generally speaking, if the relationship is good then the row is what I would call productive in the sense that, you get very upset with each other and shout and throw things around but there's some form of exchange of views and ultimately results in a reconciliation and a recognition that there is probably wrong on both sides and blablabla kiss and make up and it clears the air. But increasingly there were things that really began to upset me, and I'll go into those, and secondly when I did get upset and challenge Sarah it wasn't really possible to have, it sounds a bit silly, but a proper row. A proper row in the sense of a full and frank exchange of views and a bit of shouting but some sort of resolution resulting from it. There seemed to be no understanding on Sarah's part of what I was getting at and the responses to the points that I made when I tried to be as rational about it as I could were irrational and inconclusive. It wasn't that she just shouted and balled but she*

just, no understanding, and increasingly what the response tended to be a sort of giggle or a laugh or something. Almost as though there was a sort of a mental overload and the only way that she could deal with it was by, would be by laughing.

Steven notes both a change to the nature of disagreement and its resolution, describing his wife as responding to the disagreement by laughing. Steven mentioned such laughter several times and Steven interpreted it as a form of response to mental overload when his wife did not understand what he was trying to say. Particularly when he was expressing emotion:

Steven: *I felt that, at the time I probably thought that she was just blanking me but actually looking back it was probably just that she just wasn't able to understand where I was coming from in the broadest sense of that [term]. She had no idea why I was angry or frustrated or whatever it might be. There was not sign at all that she understood any those of things.*

Other interviewees, including "John", who had been married to his wife "Pam" for over 50 years, described similar laughter. John was a professional within the construction industry and Pam looked after the home up until the onset of FTD. John increasingly took over doing the household chores as Pam's condition deteriorated. John described Pam laughing when he became frustrated as he tried to prevent her from doing the cooking.

John : Clearing her out the kitchen could be terribly frustrating and I said to one of the women at the coffee morning, I said, 'I actually swore at Pam to actually get her out of the kitchen'. I needed to do something to get her out and she said "ahh don't worry about that I swear at James every day" (laughter) Just to, to the frustration of it, yeh

Interviewer: *And how did she respond to the frustration?*

John: *She doesn't seem to mind that much she doesn't seem to hit her personally. Water off a duck's back I think, she almost laughs you know. Shoo her out you know. I've actually locked the door I think at one point, I don't know. Push her out you know. It's, it's, well it's frustrating, it's dangerous you know.*

Though John does not give us an interpretation of why he felt his wife laughed, he does describe how his behaviour does not '*hit her personally*' and is '*water off a duck's back*'. This suggests that, in line with Steven's interpretation, John's wife either did not engage with or did not understand John's frustrations. John's description also shows a level of surprise at his wife's laughter. This was common across the reports when describing laughter during disagreement. As in John's description, interviewees tended not to simply state that their relative laughed but preceded the mention of laughter by an adverb, implying that the laughter is unusual given the context.

John: *She **almost** laughs you know*

Steven: *A **sort of** giggle or a laugh*

Surprise or disbelief at laughter fits with the laughter being inappropriate or unusual. Inappropriate laughter was particularly evident in a description provided by "Elaine". Elaine had previously worked in healthcare and education and had been married to her husband for over 30 years. She described her husband laughing during a discussion about their relationship:

Elaine: *And then one night he'd finished in the kitchen, he always does the dishes after I've cooked, and I was sitting on the settee in there and he sat beside me and he took my hand and he said 'I do love you you know' and I said 'do you? Then why do you keep telling me that you don't?' and he said 'did I? When?' and I said 'well the last time, about half an hour ago and eight times in the last eight weeks. 'Did I? Hehehee' and then he giggled like a little girl. I said 'John are you having difficulty accessing your emotions?' and he said 'Ohhh, I think there must be some confusion, hehee' and he just, he just laughed.*

Elaine's repetition of '*he just*', suggests shock or disbelief at her husband's laughter. In line with Steven's interpretation of laughter resulting from a failure to comprehend, Elaine reports her husband's laughter being accompanied by him given an apparent admission that he has incomplete comprehension of the situation saying '*there must be some confusion*'.

5.3.1.2 Physical withdrawal

An apparent failure to comprehend a disagreement was evident in descriptions of withdrawal from disagreements. “Margaret” in particular described her husband withdrawing from arguments as an early sign of FTD. Margaret and her husband had both worked in international banking and they had been married for around 50 years. Following his retirement, around 10 years previously, Margaret started to notice behavioural changes in her husband. Margaret described her husband’s reactions when she tried to talk to him about his increasing disengagement from helping her around the home:

> *Margaret: He umm, he was declining to do anything. And I could show extreme emotion because I went from asking to begging to pleading to screaming to crying to shouting at him because I felt if it, if I can get through to him: I’m very unhappy, I’m tired, I’m doing everything for you, please just help me a little bit. But I literally screamed at him, I’m sure I threw a few things, not at him but, (Laughter). And he would just look at me. Quite passive and walk out the room.*

The fact that Margaret raised this as notable highlights it as being out of character for her husband. Unusually for a heated discussion Margaret also mentions her husband being ‘*Quite passive’,* lacking in any obvious emotion. This lack of responsiveness could suggest that her husband has limited engagement with the discussion or limited comprehension of what was being expressed. Indeed Margaret later raises the question of ‘*whether he couldn’t understand*’ what she was trying to express and described how she felt that ‘*there must be some sort of mental block that I’ve got to get over’*, suggesting a common thread of failing to understand others for both laughter and walking away during conflict.

An apparent failure to comprehend what others are trying to express during disagreements was clearly described by “Stephanie”. Stephanie, a health-care worker in her early 30s, described a conversation she had had with her mother, a former housewife with SD. Stephanie described an incident when her mother had visited while Stephanie was renovating her new home. Stephanie’s mother caused a radiator to flood over a brand new carpet, at which Stephanie had become very cross. Stephanie described the conversation that she had her mother, after she had calmed down, where she attempted to explain why she had become so cross and upset:

Stephanie: *So, I sat down with her and tried to say ok, I understand it wasn't your fault and you didn't mean to. But can you understand why what you did was really upsetting. And I spent quite a lot of time trying to explain just that. Didn't get it nah, not happening. No understanding and the reason I think, she didn't get it, she would sit there and listen and look at me and then she'd say the same thing again, she'd say, 'I didn't mean it, but I didn't mean it'. It's like, ok, I understand what you're saying to me, you didn't mean it, so I understand where you're coming from. Do you understand where I'm coming from? I dadadadada really slowly, over and over. She listened to the words, she'd be looking at me and then she'd say, massive pause, as there always is with mum bless her, then she'd say but I didn't mean it, I didn't mean it. So that, might help to, this is part of the reason, it's like, it's her world, it's her, to think about, to think outside of her about anyone else and their emotion or feeling or reasoning or, reason for any of their behaviour in thoughts feelings emotions, how they come across to someone else, seems really difficult*

The description appears to show Stephanie's mother struggling to coming to an understanding of Stephanie's perspective on the situation. Due to the diagnosis of SD it is possible that impaired language comprehension may have caused part of this struggle. However, interestingly, Stephanie did not interpret the lack of comprehension as being solely due to the presence of language issues. Instead, Stephanie interprets the difficulty as being her mother not being able to think about Stephanie's point of view or consider her thoughts and feelings '*to think outside of her[self] about anyone else and their emotion or feeling or reasoning*'. Other interviewees expressed similar feelings.

"Rebecca": *He only sees a situation from his point of view now. He's incredibly selfish he does not see any situation from anybody else's point of view.*

"Thomas": *If I get annoyed and frustrated she doesn't really understand why I might be annoyed and frustrated.*

Interestingly, while many interviewees discussed their relative apparently having difficulty taking another person's mental perspective, Stephanie's was one of the only descriptions of conflict not

ending in laughter or disengagement. The fact that it was also one of the only descriptions that was not reported to involve heightened emotion may play a role in this, as could the fact that Stephanie's mother has SD.

5.3.1.3 *Tantrums*

Laughter and withdrawal often occurred when interviewees were confronting their relative with a grievance. Yet, disagreements were also described when the individuals with FTD themselves expressed a grievance. In these cases the behaviour described was very different. When the individual with FTD was asked to do something that they didn't wish to, was being criticised, or being told that they can't do something, they tended to be described as showing heightened emotion, particularly frustration and anger. While these emotions may not be unusual in such situations - anger is not an unusual response to criticism - interviewees described the emotion in ways that implied that they were taken aback by its intensity and expression. "Sandra" gave a particularly detailed description of such a scenario. Sandra met her ex-partner "Ted" at work and had known him for almost 30 years. Though no longer a couple, and living apart, Sandra still saw Ted on almost a daily basis. Sandra described Ted's response to a friend becoming ill on a walk:

> *Sandra:* *We were out with on a walk in [the town] with them and Ted just threw the most almighty tantrum and went all rigid and all sorts, and scarlet in the face and refused to move even though we were up on the ridgeway. We were miles from anywhere, we were miles from anything, and in fact what had happened, our friend "Daisy" who'd, had a brain tumour, often got epileptic fits and things, and she can cope with them and her husband can cope with them but you just have to, she sat on a stile and waited for it to pass and Ted 'Come on come on we've gotta go we've gottta go'. Tugging, tugging at us all, totally, totally, irrational behaviour like a [man] possessed.*

The description of the emotion and its intensity are both striking. To go *'scarlet in the face'* and '*refuse to move'* implies an intense level of anger or frustration that is rare in most adults. This behaviour is particularly unusual and striking, given that it is caused by a friend in distress. The use of the term 'tantrum', further highlights the presence of abnormally heightened emotion. This term was also used by "Rebecca". Rebecca's husband had worked in international business and

they had known each other for over 50 years. Rebecca described her husband's behaviour when she asked him to help her with cooking on an overseas holidays with friends:

Rebecca: *We were away in "Provence" at a friend's house and each couple cooked dinner and he wouldn't help me at all and then he threw a complete tantrum when I asked him to help with the washing up.*

The use of the term 'tantrum' implies an interpretation of the behaviour as childish. While only these two interviewees use the term tantrum, several others described behaviour that was strikingly similar, describing expressions of intense frustration and describing them as child-like.

Elaine: *It was four months later when he had started behaving incredibly childishly, he would actually pout, his bottom lip would come out and he would look like a little boy of 6. I don't know how they do it, but he would look like a little boy of 6. And he would stamp his foot, and it was the kind of childish behaviour that I didn't tolerate very frequently in my daughters and I certainly wasn't going to tolerate it in a man of his age.*

Steven: *She would get angry eventually. But it wasn't a kind of anger that manifested in her shouting back to me 'oh you're wrong about this' or 'this is the reason why I'm doing something'. It was just a sort of screwing your fists up into a ball kind of anger, what you might call a sort of truculent childish sort of anger but it wasn't... it never resulted in her explaining to me why she thought I was wrong it was just a generally just a sort of affirmation that well I'm going to do this because I want to.*

In both examples, the individual with FTD failed to articulate their frustration or anger in a relational fashion. They are described as balled up, stamping, red in the face. As described by Steven '*it wasn't a kind of anger that manifested in her shouting back to me oh you're wrong about this or this is the reason why I'm doing something'.* The examples suggest a failure of the individual with FTD to engage others in their experiences and to share why they feel emotional or what it is they are feeling in a verbal manner. In Sandra's description, while it is evident that Ted wants to keep walking, Sandra's description of '*totally, irrational behaviour*' suggests that he gave no attempt to explain the reason for his frustration. Similarly Steven described an absence of

explanation, stating that he would have expected '[his wife] *explaining to me why she thought I was wrong'*. Implying that this absence of explanation of her experience diverged from her previous behaviour. Interviewees therefore describe an apparent failure to engage with the mental perspectives of others and fail to articulate their own thoughts, feelings and emotions.

5.3.2 Sense of Humour

The second theme that emerged from the interviews was not a loss of humour in general but a change in sense of humour. Interviewees described their relatives making jokes and laughing, indeed there seemed to be a maintained tendency to find things funny. Interviewees described their relatives seemingly enjoying humour and laughter. Yet, descriptions suggested that the things their relatives found to be funny had altered.

Elaine: *I've seen him stand up and give speeches on the hoof, and he was funny. He's no longer funny, he doesn't laugh at anything anymore. He will laugh at a political joke if he makes it himself, but, but not the normal interaction, small talk that goes on in social occasions.*

Margaret: *Oh yes humour, in general, as I say it is very childish. He enjoys the adverts on the television as much as he does the programs, he can't follow programs but looking at old comedies and things like that he can laugh and laugh at that.*

Evident in these reports was a prominent reduction in the tendency to share humour: a change in the to and fro of making jokes and laughing with others. As described by Elaine, '*not the normal interaction'.* The descriptions imply that the interviewee's relatives no longer makes jokes that others find funny and no longer find the jokes of others funny.

Elaine: *These days he can't see it unless he makes a joke, which is usually, then he'll fall about laughing. And you think, 'what?' You can tell that nobody else has got it either but John will fall about laughing. Because he finds it very funny.*

Sandra: *Occasionally [he] makes, very occasionally [he] makes a joke and I'll go 'ohhhhh' and then he made a joke and laugh and he'll look quite pleased he's made a joke.*

The sources of humour for individuals with FTD were described as being primarily silly things and their own jokes. Elaine explained how a friend described her husband's humour as 'Fatuous'. This term fits the general reports of humour very well and is exemplified nicely by Sandra's description of her ex-partner's laughing at her cat.

Sandra: *He often laughs at something, the cat might do… although if she's sick all over the chair and all the crevices and all over the files, and all over the floor and I have to clean it up there's no, he's impassive then. But if she's got her tongue hanging out or something he'll sort of smile and laugh a bit.*

In a similar fashion to the behaviours described in relation to tantrums, several interviewees explicitly described the sense of humour of their relative as childish. Margaret describes her husband's sense of humour as '*very childish*' and Steven described his wife as taking pleasure from telling *'nappy humour sort of stories'*. Margaret gave the following example of a brief joke that her husband regularly makes and finds very funny.

Margaret: *If anyone says "see you later" it will always be "alligator, in a while crocodile"*

Interviewer: *oh really!*

Margaret: *To EVERYBODY (Laughter)*

Interviewer: *And does he find it funny? Is that kind of amusing?*

Margaret: *Oh yes! Helaaaarious (Laughter)*

This increased childishness was strikingly matched with an absence of what may be described as more 'adult', sophisticated, forms of humour such as verbal exchanges involving figurative language, that is, utterances in which the literal meaning of the utterance is not the same as their intended meaning. Examples include sarcasm, double entendre and facetiousness. A prominent change in sarcasm was noted by Margaret '*Anything with a slight bit of sarcasm or umm, double entendre, no he would never see it*' and Sandra described her ex-partner failing to comprehend facetiousness when she described him asking her what to write in a greetings card:

Sandra: *Normally I'd get him to sign the card, I'd say oh can you sign this for so and so's birthday or something, but, he won't say, he won't even look at the card, and he might put, he'll say to me what shall I say? So I'll say why don't you write 'bugger off Christine' or something on it and he doesn't kind of understand that I'm being facetious, so I just put, why don't you put' love from Ted or something?'*

Such a misinterpretation of non-literal humour appeared to extend into misinterpretation of the behaviours and acts of others in an example given by Elaine:

Elaine: *When my middle granddaughter, about three years ago, got the highest marks in the land for mathematics and something or other they sent her a letter to say you've got the... and my daughter e-mailed a scan of this letter, we'd all seen it. Well her brother came home that evening and he's a bit of a wise cracker, he mocked up a, same letter, saying, there's been a terrible mistake, I'm so so sorry you actually got the worst marks. And we laughed ourselves silly. But I brought John in then and [he said] sort of oh that's very serious, I said 'john no no it's a joke', 'yu, yu yes but it's very serious' I said 'john, it's a joke, [her nephew] wrote this letter', 'no, no, but it's very very serious'… he just could not get it at all.*

Consistent with the idea that figurative speech was being misunderstood, several interviewees describe their relative as taking sarcastic comments literally. Margaret described a situation where her husband was being mocked but failed to appreciate the sarcastic tone:

Margaret: *I do remember one time when, I suppose there was something slightly amiss and people were making fun of him. I could pick it up straight away that somebody was, being a bit unkind really. But he could not see that, he took what they said absolutely literally, which of course just compounded the error.*

These literal interpretations imply a failure to understand the double meaning. There appears to be no engagement with the fact that what the others are saying may not be the same as what they are thinking, and that this disconnect may be humorous. Thus while a sense of humour is clearly present, it appears rather simple, childlike and egocentric, based on novel or silly things. Far less

engagement was apparent in interactive humour and particularly that based around playing with the expectations and understanding of others, such as humour involving figurative language.

5.3.3 Apparent deception

A prominent and novel theme identified within the transcripts was the presence of apparent lying and deception. This is a particularly interesting because of the complex social dynamics that may be involved in these complex behaviours.

5.3.3.1 *Lies*

Though lying is a pervasive social behaviour, what was unexpected was that so many interviewees would mention their family member apparently to lie to them. Interviewees also notably described an increased frequency of apparent lies.

Rebecca: *Now all of a sudden I would think that has happened in the last six months, it is becoming increasingly obvious that he is confabulating. I would go as far as to say on occasions lying. Using any anything to put the blame on somebody else that has caused the problem.*

Sandra: *Tells all sorts of things that are just not true. Tells lies quite often.*

Samantha: *Ahhh, in many ways I was a bit naive and, for a lot of the time I would believe him. Well I would hope that what he was telling me was the truth rather than believing him. Because he never lied, it didn't occur to me that he was lying until, you know, as things progressed*

The lies may be best described as simple self-protective lies, lies told when the interviewee's relative knew that the truth would lead to an outcome that they didn't want. As in Rebecca's description above, lies were often described as occurring to apparently cover something up or to avoid blame for a transgression. Behaviours fitted into two general forms, lying – generally speaking inaccuracies to apparently attempt to avoid an outcome, and deception – acting in a way that may not provide or hide information to avoid the outcome.

What is notable is not necessarily that the family members are lying per se, but that interviewees are aware of apparently being lied to. This is interesting because the benefits of lying are based in deception. An increased awareness of lies on the part of the lie recipient thus suggests that the ability to produce believable lies may be diminished. Several examples of ineffective lies were provided by Samantha. These examples suggests the apparent lies were ineffective because Samantha's husband was failing to understand what would be believable for Samantha, to account for her point of view and background knowledge when he was formulating his lies:

Samantha:

(1) He'd also asked me to get him some Viagra. And I said well we haven't used them. Where have they all gone, 'well they were destroyed in the fire'. I said 'no they weren't, I know they weren't'. So this lying, and getting himself deep into trouble.

(2) He went up to that re-union and he was strange when he came back, and I can understand why, memories back that had been stirred up. But then, about 4 or 5 months later he said he was going to a school reunion but I said 'but you've just been to one'. 'No I haven't' [he replied].

(3) He said 'umm, she's been, she's been made redundant' and I said 'that doesn't make sense', he said 'why doesn't that make sense', I said 'because you said she was self-employed.' and I said 'if she was employed and if she was being made redundant she would have a payout.' You know. So. Ah, lying was, just awful. Just awful.

Samantha appears to feel that her husband may be lying to her because what he is saying doesn't fit with facts that she knows to be correct. This is presumably also the case with Rebecca's husband as she explains that '*it is becoming increasingly obvious that he is confabulating'.* No examples were however provided by either interviewee to allow for an interrogation of this presumption and what may have led her to come to this conclusion.

5.3.3.2 Apparent Deception

Apparently deceptive behaviour was less frequently described than individuals appearing to lie, however interesting examples of deception were given. For example Rebecca described her husband trying to have more alcoholic drinks than she wanted him to:

Rebecca: *I don't mind him having a couple of whiskies with lots of, tumblers full of water. But while he thought I was pre-occupied with everything that was going on that completely threw him he was sneaking whiskies in and when I saw him sneaking what was about his fourth. I just took the bottle away and I said there's no more for you. He said it's fine for you, you can have a drink and I'm not allowed one. Controlling me again.*

Interviewer: *Right Ok, So he's aware of the fact that you don't want him to do that and was so was he trying to, he was doing it when you weren't in the room, those kind of*

Rebecca: *Yes, he he he, because of the reflection in the conservatory you can see. So he thought round the corner or I was busy that he could do it, so he'd just go and sneak it, and he's been doing that for years.*

Interviewer: *Ok, so he would knowingly not do it if you were in the room*

Rebecca: *Absolutely, I think you're probably right. It would always be done surreptitiously, if he thought he was over the two that he's allowed.*

Rebecca's example shows that her husband is aware of her attitude towards his drinking but that he apparently fails to appreciate all aspects of the situation to effectively conceal his behaviour. Here it is unclear exactly why Rebecca's husband is failing to effectively conceal his behaviour. Samantha however, provided several examples of apparently failed attempts at deception that suggested that a failure to consider the mental perspective and knowledge of others. This was particularly evident in descriptions of her husband hiding money and having telephone conversations with another women.

(1)

Samantha: *He would tiptoe, he would go out of this door and he would, this is outside with the door shut, I'd look out of the window and I would see him tiptoeing to where he'd have it [his mobile phone] re-charged. Now, ahh, again there's absolutely no insight into the fact that I could have been you know, it just incredible.*

Interviewer: *It's an interesting combination, to know that you're doing something that, you're being secretive, so you tiptoe, but not quite understanding that in this context tiptoeing is not the appropriate thing to do because that makes it look more suspicious.*

Samantha: *(laughing) yep, you're ab, actually it's lovely talking to you because you're absolutely right, you know. You don't tiptoe through mud*

(2)

Samantha: *Andrew didn't hide his phone but he found my phone and erased the ones [text messages] that she'd sent to me, so there was, there was a low cunning flying around. Which actually is not, I don't think is totally unusual with the, with this.*

In both examples, the behaviour described fits with an intention to conceal, but shows a failure to appreciate Samantha's knowledge and how things look to her. Similarly to how speech that appeared to as ineffective lies included information that others know to be false, there appears to be a failure to consider the knowledge of others when attempting to conceal behaviour. For example, there is little point deleting messages that have already been read especially as Samantha stated that she could access her husband's phone, making it relatively redundant to delete similar messages on her phone. Interestingly, to tiptoe implies being aware that others may hear you and that you are trying to conceal your movement; yet, to tiptoe here shows a misunderstanding of what may look suspicious – in this situation simply walking would be far less conspicuous. These examples suggest that there may be changes present in both lying and concealment and that in both cases interviewee's relatives fail to account for others' perspectives and knowledge.

5.4 Discussion

The aim of this chapter was to utilise family member narratives of social behaviour change in FTD to explore the dynamic, contextual and interactional nature of social and empathic behavioural change in FTD as it manifests in the real world, as opposed to in the laboratory. A particular focus of this work was on spontaneous, interpersonal, interactions that take place inside the context and privacy of an interactional dyad's everyday life, behaviours that are inaccessible using standard experimental methods. As well as describing behavioural change in more detail than currently present in the literature it was hoped that consideration of commonalities amongst identified themes in this work would lead to novel hypotheses on the cognitive changes that may underpin social behavioural changes in FTD.

Within the findings section there was intentionally sparse commentary and interpretation of the data to allow for a more open qualitative consideration, without imposed interpretation. Grounded theory does however allow for the incorporation of existing experimental work and theory in the consideration of data (Charmaz, 2006). Therefore the data will now be interpreted in relation to existing knowledge of social cognitive functioning in FTD.

5.4.1 Connecting the identified themes: problems with everyday mentalising

A failure to consider or understand the views and knowledge of others could play a potential role in, and thus help connect, all three emergent themes: *disagreement during conflict*, s*ense of humour* and A*pparent deception*. As discussed in previous chapters, mentalising is the attribution of mental states (e.g. thoughts, feelings, beliefs) to others. Experimental studies reveal that mentalising is altered in FTD (Bejanin et al., 2017; Bora et al., 2015; Henry et al., 2014); see previous chapter), however little or no work has considered in any depth day-to-day mentalising, an ability that may be particularly important within close committed relationships (Dodell-Feder, Felix, Yung, & Hooker, 2016). The three themes identified here were constructed through an inductive grounded theory approach, selected for their prominence, early appearance and social nature, yet they may also be a first description of everyday examples of behavioural changes attributable to changes in mentalising in FTD.

5.4.1.1 Conflict resolution

In pre-school children the ability to reconcile after conflict has been associated with the ability to consider the mental perspectives of others (Dunn & Herrera, 1997; Liao, Li, & Su, 2013). In children the method of resolving of conflict, rather than the frequency of conflicts per se, appears related to mentalising ability (Dunn & Herrera, 1997). Children with more mature mentalising skills are more likely to negotiate and to ask others for their perspectives when attempting to resolve conflict (Dunn & Herrera, 1997; Liao et al., 2013). In addition, in adult relationships, "empathic accuracy" (defined the extent to which partners understand each other's unspoken thoughts or feelings as they spontaneously occur during the course of their everyday interactions, i.e. mentalising) has been linked to accommodative behaviour following marital conflict (Bissonnette, Rusbult, & Kilpatrick., 1997).

Alteration of mentalising could be particularly salient during conflict as it may be one of the few times where it is clear that viewpoints, beliefs, feelings or intentions differ. It thus seems feasible that a change in mentalising may contribute to changes in conflict resolution described here. Indeed, several interviewees explicitly stated or suggested that they felt that their relative was unable to understand their perspective when discussing disagreements or to consider the thoughts or feelings that they were trying to convey. While difficulty in sharing one's own viewpoint is not unusual in its self, the failure to engage in discussions and attempt to understand or communicate viewpoint differences seems likely to be unusual for well-established couples. Given the importance of responsiveness in long term relationships (Reis & Gable, 2015) it would be surprising if these couples have always been so unable to resolve disputes and yet still have such enduring relationships.

The descriptions of tantrums are consistent with an inability to take into account the viewpoint and knowledge of others. Interviewees described their relatives failing to explain their own viewpoint or the source of their dissatisfaction during 'tantrums'. This could be related to an impaired ability to mentalise, as it could be due to an inability to reason about and reflect on one's own mental states, argued by some to involve the same system as the ability to consider the mental states of others (Decety & Grezes, 2006; Happé, 2003; Mitchell, 2009; Saxe, 2009). Further to this tantrums could be due to a failure to comprehend that others hold different views to oneself. In both cases, a lack of mental perspective taking could lead to the frustration that results

in a 'tantrum' because of a limited comprehension of why others aren't behaving as wanted or expected. Notably, an increased frequency of tantrums has been observed in individuals with ASD, a condition often associated with impairments in mentalising (Baron-Cohen, 2000).

5.4.1.2 Sense of Humour

Regarding humour, interviewees described many misunderstandings of comments that involved figurative language, a form of humour reliant on understanding the beliefs and views of others (Kline, Gallee, Balewski, & Fedorenko, 2017). Understanding figurative language relies on mentalising as it requires the identification of the communicative purpose of the speech (Demorest, Silberstein, Gardner, & Winner, 1983; McDonald, 1999). Processing of contextual information is necessary for inferring the communicative purpose of speech and has previously been proposed as an explanation for the pattern of social cognitive impairment seen in FTD (Ibanez & Manes, 2012) and as an explanation for changes in humour in FTD (Clark et al., 2016; Clark, Nicholas, Henley, et al., 2015). Yet, context comprehension per se is unlikely to be sufficient to explain the behaviours observed here. Instead it seems more likely that altered mentalising may underpin difficulties in the comprehension of the communicative intentions of speech (Cummings, 2015). Hence, if mentalising is impaired, then the alternative meaning of the comments will be missed and comments taken literally.

Existing work supports the proposal that the comprehension of figurative speech may be reliant on mentalising. In children with ASD, mentalising ability predicts the comprehension of both metaphor and irony (Happé, 1993): those with lower levels of mentalising ability showed literal interpretations of irony. Mentalising skills are also related to the comprehension of deceitful speech in children (Bosco & Gabbatore, 2017). Consistent with mentalising having a key role in social humour, activity within brain regions associated with mentalising shows sensitivity to linguistic jokes (Kline et al., 2017). Impaired mentalising resulting from RH brain damage has further been associated with an impaired ability to distinguish between lies and jokes (Winner, Brownell, Happe, Blum, & Pincus, 1998) and with impairments in sarcasm comprehension (Channon, Pellijeff, & Rule, 2005). This suggests that 'getting' a joke and engaging in social humour may indeed rely on mentalising and the comprehension of the beliefs and intentions of others.

The relationship between humour, figurative language and mentalising has not been directly studied in FTD. An inability to distinguish lies and jokes has however been observed in FTD (Rankin et al., 2009). Yet it seems likely that impaired mentalising played a key role in the behaviours observed here, as sarcasm comprehension in FTD relates to performance on assessments of mentalising (Shany-Ur et al., 2012). Similarities are also present between the descriptions of behaviour described here and descriptions of behaviour given in other groups where a link has been made between mentalising and humour or figurative speech. For example, individuals with disturbed social behaviour following traumatic brain injury show literal interpretations of sarcastic comments and mock praise (Channon et al., 2007; McDonald, 1999). Similarly in an observational study, children with ASD failed to laugh at social humour or to join in with the laughter of others (Reddy, Williams, & Vaughan, 2002). The children instead found strange scenarios humorous (Reddy et al., 2002). ASD is often associated with impairments in mentalising (Baron-Cohen, 2000; Murdaugh et al., 2012), though there is ongoing debate over whether impairments in the comprehension of figurative speech are related to mentalising ability in ASD (Kalandadze, Norbury, Nærland, & Næss, 2016; Vulchanova, Saldaña, Chahboun, & Vulchanov, 2015). The striking similarities between humour and figurative speech comprehension in these three groups with atypical social behaviour (FTD, ASD, TBI), all posited to have a prominent impairment in mentalising, suggests that comprehending the communicative intent of others may well play a role in humour and figurative language.

5.4.1.3 Apparent deception

Though changes to disagreements and humour may imply the presence of altered mentalising, they do not clearly indicate whether this change lies in the ability or the propensity to mentalise (Keysers & Gazzola, 2014). Considering the descriptions of deception however provides a way of separating the two.

Ability and propensity may be separable facets of social functioning such that individuals may be capable of understanding others but choose not to, or vice versa (Keysers & Gazzola, 2014). An issue with separating these two components is that behaviour could be much the same for individuals who wish to consider the mental state of another but are unable to so and those who can understand others but chose not to. Descriptions of humour and disagreement suggest that deficits reside in the ability to perspective take: it would be hard to explain why there would be a

change in humour based on changed interest in perspective taking. Some descriptions also suggest that the interviewee's relative may wish to understand others, for example, Stephanie's mother sits and apparently listens to her daughter explaining why she was cross; Elaine's husband takes her hand and apparently affectionately says '*I do love you you know'* shortly before laughing at their disagreement. Yet, it is not possible to conclude based on these descriptions that the behaviours were not occurring as a result of a disinclination to consider the perspective of another. Perspective taking in these situations is broadly to the benefit of the individual whose perspective is being taken. Therefore a lack of concern for others or diminished interest in maintaining social cohesion could result in a lack of intention to perspective take.

Deception may provide a clearer view of the separation between ability and propensity to perspective take, as only where we know that there is an *intention* to consider the thoughts or feelings of another can we be confident that any impairment lies in the ability to mentalise. Unlike humour and conflict, deception is highly dependent on understanding others, yet is generally to the benefit of the individual doing the perspective taking. Deception is reliant on mentalising firstly because to attempt to deceive requires an understanding that others can hold a false belief. Tests of false belief comprehension form classic assessments of mentalising (Achim et al., 2013; Gopnik & Astington, 1988; Wimmer & Perner, 1983) and false belief understanding is related to false denials of wrongdoing in pre-school children (Polak & Harris, 1999). Secondly, deception requires the manipulation of the viewpoint or knowledge of others. Such manipulation may require individuals to mentalise to determine what another knows and believes, in order to formulate verbal and non-verbal behaviour to lead the target to the desired false belief or misdirection of attention. Therefore the inability to formulate an effective deception despite an apparent desire to deceive is evidence for a maintained intention to perspective take but impaired ability to do so. As the reports suggest a desire to deceive, but ineffective deceptions, they suggest a genuine impairment in the ability to mentalise.

5.4.1.4 Interim summary

The three themes presented may all represent scenarios where changes in the ability to perspective take or mentalise may cause behavioural change in FTD. The presence of these behaviours alone is not being argued to be indicative of FTD, as they clearly occur in the general population. Yet it is notable here that these behaviours were commented on by multiple

interviewees from different walks of life, locations in the UK and both men and women, each of whom highlighted the described behaviours as being a change from premorbid character and thus most likely disease relevant. Together, the outlined behavioural changes are likely indicative of problems in mentalising in FTD. The fact that all three themes that emerged from an inductive analysis may plausibly depend on mentalising highlights the likely salience of the behavioural impact of mentalising impairments in FTD in close relationships.

5.4.2 Childishness

It was notable that within the reports, several behaviours were interpreted or described as 'childish'. This was particularly noticeable in the discussion of both disagreement and humour. This seeming childishness highlights an apparent regression within the symptoms of FTD where by developmentally late maturing social abilities including complex mentalising (Blakemore, 2012) seem to alter early on in disease ("first-in-last-out"). That is not to say that this represents a true retrogenesis or return to a child-like state (Yeatman, Wandell, & Mezer, 2014). Rather, in FTD there is selective vulnerability of a late-maturing neuronal system important for complex social cognition (Seeley, 2008).

Changes to the ability to perspective take may lead to behaviour that seems child-like because the ability to formulate accurate inferences about others is not fully developed until adulthood (Blijd-Hoogewys & van Geert, 2016; Frith & Frith, 2003). The ability to make increasingly complex mental state inferences develops across childhood and thus differences are seen across development in how children formulate lies (Polak & Harris, 1999) and resolve disputes (Liao et al., 2013). Behaviours that show more basic mental state understanding may seem childish as they may be most commonly seen in younger children. Figurative language may seem 'adult' as it is rarely used by children: comprehension of figurative language is not seen until the age of around 11, before which it is interpreted literally (Demorest et al., 1983). As such literal interpretations of figurative speech described by interviewees may appear childlike. Whilst attempts at deception were not described by interviewees as childlike, they were strikingly similar to the kinds of deception shown by children, such as simple denial of wrongdoing (Polak & Harris, 1999). Behaviours revealing impaired mental state inference in FTD may therefore be described as child-like, as the late

development of complex social cognition means that these behaviours are most commonly seen in children, and hence child related language is what we have to describe this behaviour.

The language used to describe behaviour may both influence and be influenced by the changing dynamic of the interviewee's relationship with their family member. Interviewees reported doing an increasing number of tasks for their relative with FTD and restricting their day to day activities and access to things such as alcohol or medication. Many of the interviewees were acutely aware of the impact of this on their relative with FTD's autonomy. These actions were seen as necessary for the safety of their relative with FTD and management of their situation. Yet with limited insight into their own behavioural changes, individuals with FTD may take issue with limitations being placed on their autonomy and thus take issue with changes to the relationship dynamic. Deception, for example, was frequently described when the individual with FTD clearly knew that they are not 'meant' to be doing something and thus may have felt disempowered and patronized. The restriction of behaviour described and the language used may be consistent with the infantilisation of individuals with dementia, previously described as being shown by individuals in positions of authority (Marson & Powell, 2013) and care (Caporael, 1981; Williams, Herman, Gajweski, & Wilson, 2009), and which has been shown to precipitate "problem" behaviours (Williams et al., 2009). The descriptions provided here further suggest that family members as well as professionals may develop 'social interaction scripts' (Marson & Powell, 2013), which may lead to infantilisation. Taking over responsibilities and control of others' behaviour could be seen as infantilisation and may lead to the relationship dynamic becoming more akin to that of parent and child (Williams et al., 2009). Interviewees expressed feelings of protection and concern for their relative, suggesting that infantilisation may occur due to uncertainty over their relative's judgement and competence. Interestingly, in line with this, reports suggested the interviewee's relatives resisted many restrictions being put on their autonomy, resulting in friction, which is somewhat akin to that seen in children and adolescents, Individual's whose autonomy is restricted more frequently than that of most adults (see also Williams et al., (2009)). As such it may be unsurprising that responses to restricted autonomy may be perceived as childish. Such bidirectional influences speak to the strength of the current approach for the study of social behaviour change in FTD.

5.4.3 Limitations

Clearly, social behaviours involve the ongoing interaction of at least two parties. A limitation of the data presented here is that it includes the perspective of only one interaction partner. A single perspective cannot capture all aspects of a dynamic social interaction, as different parties may interpret situations differently. Having only a single perspective could lead to some aspects of the apparent lack of viewpoint taking described. Simply because an individual feels that they are misunderstood or that another doesn't share their viewpoint, does not necessarily mean that this is in fact the case. As such, we cannot know from only the interviewee's descriptions whether there was any attempt to perspective take/mentalise or not. Behaviours such as lying could emerge because individuals genuinely hold different beliefs. This may be particularly likely to occur with individuals with FTD, who are known to have issues with memory and insight (Hornberger et al., 2014; Irish, Graham, Graham, Hodges, & Hornberger, 2012; O'Keeffe et al., 2007) and may therefore unintentionally speak inaccurately. This could not, however explain the altered humour or deceptive behaviours. As no external observer can truly know the intentions or mental state of another, only obtaining a self-report from individuals with FTD would overcome this issue. This is however unlikely to be feasible as there would be ethical issues with discussing the events described here with the individuals with FTD themselves. Further to this, it is entirely likely that historical events such as these may not be recalled by the individuals and because individuals with FTD have profound impairments in insight they may struggle to reflect on themselves and their experiences (O'Keeffe et al., 2007). As such close family members remain some of the most reliable informants to infer the intentions and thoughts of individuals with FTD. Future work involving individuals with FTD themselves would be of value but would have to be approached with great care, delicacy and tact.

The involvement of the interviewees in the interactions described will have had a substantial impact on the results, since it is hard to be entirely objective about interactions that we ourselves are involved in (Ickes & Simpson, 1997). The interviewee's relationship with the individual with FTD is a major strength of this work: their rich knowledge concerning their partners' idiosyncrasies is likely to direct attention to even very subtle alterations in behaviour, yet it also brings with it bias. The social and emotional involvement of interviewees with the topics of discussion means that thier descriptions and interpretations will be influenced by their wants, beliefs and emotions

(Ickes & Simpson, 1997). In addition, the changing nature of their relationship with the individual with FTD will further impact on their reports. For example, behavioural changes were described as leading to interviewees feeling less sure of their relative and feeling that they don't know them anymore. Such changes in perceived identity have a huge impact on relationships (Strohminger & Nichols, 2015). Interviewees described no longer giving their relative the benefit of the doubt and increasingly doubting the truth of what they said. This heightened state of suspiciousness and mistrust could lead to some of the perceived alterations described. For example interviewees may feel more often lied to irrespective of the actual frequency of lies. Such effects however seem unlikely to explain all the behavioural changes described by the interviewees.

It is worthy of note that some reported behavioural changes could be occurring as a result of changes in the dynamic of the relationship between interviewee and their relative with FTD. Behavioural changes caused by FTD *and* the diagnosis of FTD may both affect the behaviour the individual with FTD and that of their family members, which in turn could further influence the social behaviour of the individual with FTD. As described above, the presence of a diagnosis could lead to infantilisation or doubt in the reliability of what is said by the individual with FTD, which could impact on the behaviour of both the individual with FTD and their family members. Some behavioural change may thus occur as a result of the change in the relationship dynamic. Deceptions, tantrums and walking away during disagreement may all represent attempts to maintain some level of autonomy in situations where autonomy is restricted. Individuals with FTD may retain some awareness of changes in how much trust their partner places in them and what they say, despite insight and perception changes. This may alter the dynamic of the relationship and compound behavioural change (Williams et al., 2009). This does not impart responsibility to families for behavioural change (such altered dynamics are inevitable when pronounced behavioural changes occur) but it is important to recognise that behavioural alterations occur in a relational dynamic which involve multiple parties. Behavioural change will thus not just be influenced by change in the individual with FTD, but also by changes within the relationship dynamic. This could explain for example, why some behavioural changes are reported as being clear to family members and not to even close friends.

The nature of the behaviours described will have been influenced by the demographics of the interviewees. The interviewees were of a limited demographic: all were white British, most were over 60, well educated, and from professional households. Interviewees were also

disproportionately the wives of male individuals with FTD. Demographic factors will have impacted on the nature of the dynamics of conflict, conflict resolution, humour and deception described. For example, many of the behaviours that have been argued to reflect attempts to maintain autonomy were described by women in relation to their husbands. Autonomy has been described as a central component of relationship dynamics and as having a higher importance for males than females (Illouz 2012). From a sociological stand point, the desire for autonomy will be greater in individuals for whom such autonomy is typical (Niemeyer, 2013). A greater drive for autonomy in males in their 60s in 2017 may fit with typical gender roles of this demographic of older, highly financially and professionally successful men. Threats to autonomy may therefore be met with a particular backlash from this demographic. Similarly, humour is highly culturally bound and sarcasm, double-entendre and facetiousness are prominent forms of 'British' humour. As such these may be particularly salient for British people. A change in sarcasm comprehension has however been reported in FTD both in the USA (Rankin et al., 2009; Shany-Ur et al., 2012) and Japan (Matsui et al., 2016). It thus seems likely that while demographics may alter the prominence or salience of the behaviours reported, their occurrence per se may not be culturally specific.

As several of the limitations outlined suggest that some aspects of the data may relate to the demographics of the individuals and the presence of disease more generally rather than bvFTD specifically, it may be desirable to follow up this work with a similar study in an alternative though similar group, such as individuals with AD. While the use of a control group is not standard practice in qualitative work, the completion of a similar study with the family members of individuals with AD may allow for a comparison across groups that may allow for more definitive conclusions to be drawn regarding whether some of the changes in behaviour reported here do indeed relate to the presence of behavioural symptoms of bvFTD or whether they may be more general consequences of changes in established relationships due to the presence of a diagnosis of neurodegenerative disease.

5.4.4 Strengths of Qualitative work

A great strength of the method was used here that it allowed for family members to contribute to research. The active contribution of family members to this work and the focus on their perspectives means that the changes discussed in this data represent what these individuals felt to

be some the most important changes affecting their family dynamics and wellbeing. A great strength of this work is the description of these views and experiences, which are rarely reported or utilised in research, since family members are rarely given the freedom to report what they feel to be important rather than respond to predetermined questions. By highlighting prominent changes for families this work could help to direct the development of future assessments for early detection of behavioural changes and of psycho-educational interventions to support families.

As discussed, a strength of this method is that unlike typical laboratory assessments, it focuses on spontaneous interactions that take place inside the context and privacy of everyday life. As such it has greater ecological validity than standard experimental methods. Close relationships involve potentially unique forms of social cognition and knowledge, in both partners, relative to other social interactions (Welborn & Lieberman, 2015). By ignoring this rich source of information researchers may miss diagnostically useful behavioural changes. The focus on the unique knowledge of the interviewees is a strength of this work over previous observational work as not all-social behaviour can be interpreted or understood by outside observers.

The interactional nature of the interviews allowed for a shared exploration of behavioural changes rather than just a report from the memory of the interviewee. As such, domains were covered that may not have not come up in a simple report of symptoms. The detailed nature of reports also allowed for analysis to go beyond the simple presence of changes to a consideration of potential interpretations of the behaviours. For example the apparent regression and perceived childishness were primarily evident because of the possibility to consider the nature of the behaviours described and the language used to describe behaviour by interviewees. This allowed for a consideration of how relationship dynamics may be changing and influencing reported behavioural changes. It also provided a novel line of evidence in support of a change in mentalising in FTD. Importantly, this was not an inevitable outcome of the work, as it was based on an inductive methodology (grounded theory).

5.4.5 Reflections on the methodology

Rich qualitative data requires a very different approach to quantitate data and presents many ways to interpret findings. Qualitative work is intrinsically inductive and exploratory rather than

deductive and confirmatory. This presents a challenge as such work results in many more themes than can be explored, presenting the issue of how to select themes to focus upon. This apparent freedom to select data is counter to many of the principles of quantitative research and may thus seem dubious to those primarily familiar with quantitative work. Similar processes, however, are in action when personal interactions with patients inevitably drive researchers' beliefs about the disease, and subsequently their research. The advantage of the work presented here is that impressions are formulated in an intentionally systematic and reflective way. This said, all analyses are fallible and are implicitly imbued with biases, such as confirmatory biases, which may drive impressions to reinforce what has already been learned about the disease. While qualitative work is not immune to bias, its strength it in that it is intentionally alive to these biases and reflective of their impact (Charmaz, 2006).

Unlike quantitative methods, qualitative work is not intended to be generalisable but represents the experiences of a small sample of individuals. Generalisation of these results to the wider FTD population would thus be inappropriate, especially given the inclusion of both SD and bvFTD in this work. Being hypothesis free the findings from this work can however be meaningfully used to inform and develop theory. This is a major strength of this work as qualitative work is established as a strong foundation for the formulation of theory and development of quantitative assessments (Fine & Elsbach, 2000). In the development of such theory, care must be taken to achieve a balance between interpreting reports to extract the most meaningful analysis and not over-interpreting the data. Yet, this is not unique to qualitative work, simply more overt. Thus while the findings here cannot be generalised they present several avenues for the development of further investigations.

Unfortunately memory is fallible and as such we cannot know how closely interviewees' reports reflect the true behaviour of the individuals with FTD. Yet this may not be a fundamental issue as part of the value of this data is the interpretation of the behaviours that were made by the interviewees. The interpretation of the second party within an interaction is a critical component of the interaction. Indeed to understand how FTD affects families and identify diagnostically relevant behaviours, the experience and interpretation of behaviours made by family members may in some ways be of more importance than the behaviours themselves (Reis & Gable, 2015). The relationship-relevance of the changes identified here are a strength of this work. It is unlikely to be coincidence that arguments, humour and deception are all key themes of relationships and

factors such as conflict resolution style are known to influence relationship maintenance and quality (Du Rocher Schudlich, Papp, & Cummings, 2004; Gottman & Levenson, 2000). It seems entirely reasonable that behaviours where changes are most obvious in FTD are those that have the greatest impact on the quality of all close relationships.

Despite its strengths, qualitative research is not suitable for the investigation of all behaviours. During these interviews, several interviewees discussed emotion perception, however across all interviews insufficient data was present for a meaningful analysis to be carried out. Though elaboration was sought on expressions of emotion and understanding of the expressions of emotion produced by others, interviewees struggled to describe these behaviours in sufficient detail for insights to be gleaned. This may be due to the linguistic challenge of accurately describing nonverbal communication, including facial expression and vocal tone and suggests that changes in paralinguistic emotion expression and comprehension may not be especially well suited to qualitative investigation using narrative methods. Quantitative and observational methods may be better suited to the investigation of changes in the production and comprehension of emotion expression. Narrative methods may be better suited to the investigation of high-level, language mediated social cognition, such as mentalising.

5.4.6 Implications for Empathy

This work has several important implications for our understanding and consideration of empathy, beyond FTD. Firstly, this work highlights that the cognitive component of empathy may have a key role in a wide array of social behaviour. A critical consequence of this is that it emphasises the breath of empathy relevant behaviour and highlights the very narrow scope of much empathy research. While, as discussed in chapter 2 in particular, perceptual components of empathy may have an important role, they fail to encompass much of naturalistic everyday empathising. Yet, many experimental studies focus on perceptual components of empathy, particularly the understanding the experiences of others based on observation, and as such this may result in a skewed literature on empathy which does not accurately reflect the breath of naturalistic empathising. This work thus highlights the importance of considering empathy as a wider set of behaviours, potentially moving away from the focus on responsiveness to expression of emotion. Instead, this work suggests that a consideration of behaviours such as humour or dishonesty may

be sensitive to specific components of empathy and consideration of them may therefore provide an insight into empathy.

5.4.7 Conclusions

The aim of this work was to provide a detailed consideration of social changes in FTD. It was envisaged that qualitative reports would help identify behavioural changes that are prominent, diagnostically sensitive, impact upon family wellbeing and which may provide an indication of what cognitive changes may underlie social behavioural alteration in FTD. A detailed description was provided of three themes of behavioural change identified from family member interviews. A consideration of the themes suggested that a change in mentalising may underlie some of the most prominent changes in social behaviour in FTD, consistent with laboratory based studies of social cognition in FTD (Bora et al., 2015; Henry et al., 2014). The data further shed a light on how such alterations may contribute to burden and distress felt by family members. These social behaviour changes were further highlighted as leading to an increasing interpretation of individuals with FTD as childish, consistent with a retrogenesis-like account of behavioural change (Reisberg et al., 2002).

The work here may be of utility for directing the future development of measures of social cognitive functioning with increased sensitivity to the presence of FTD. This work suggests that a lack of shared humour; more noticeable deception and impaired figurative language comprehension (e.g. sarcasm, irony); are strong candidates as early behavioural indicators of FTD. Changes in humour were noted as some of the earliest changes observed, consistent with recent work that has reported a reduction in appreciation for satirical comedy appearing between 2 and 13 years prior to the onset of typical symptoms of FTD (Clark, Nicholas, Gordon, et al., 2015; Clark et al., 2016). If these changes are indeed a result of changes in mentalising, then this may further suggest that changes in mentalising are some of the earliest changes in FTD, and that early FTD may be a useful clinical paradigm for studying the neural substrates and functions of advanced mentalising abilities. Future work should attempt to develop assessments of humour, deception and figurative language comprehension that can be analysed quantitatively.

A final and important contribution that this work makes is to highlight the valuable contribution that family members of individuals with FTD can make to the understanding of FTD, when their

unique knowledge is actively included in research. The understanding gleaned from this work could lead not only to a better understanding of social cognitive and empathic functioning but also improved diagnostic assessments and the development of targeted support for families. This work indicates that it is important to take a multi-pronged approach to understanding social cognition, involving interviews and narratives, observation and experimentation.

6

General Discussion

6.1 Overview

Empathy is a complex interpersonal ability, which is generally agreed to be multi-faceted (Blair, 2005; de Waal & Preston, 2017; Decety & Cowell, 2014; Shamay-Tsoory, 2011) with a general consensus on the presence of (at least) two, partially separable systems, generally described as cognitive and affective empathy (Davis, 1983; Decety, 2011; Decety & Jackson, 2004; Shamay-Tsoory, 2011; Shamay-Tsoory et al., 2009; Zaki & Ochsner, 2012). Previously, these systems have been considered in terms of their cognitive and regional cortical underpinnings (de Waal & Preston, 2017; Decety, 2011; Dziobek et al., 2008; Preston & de Waal, 2002; Shamay-Tsoory, 2011; Shamay-Tsoory et al., 2009; Shamay-Tsoory et al., 2004). Yet, despite evidence from lesion patients indicating dissociation of the neural circuits supporting each component and involvement of white matter structures in each component (Herbet et al., 2014; Herbet et al., 2015; Shamay-Tsoory et al., 2009), relatively little work has considered empathy from a brain network-level perspective or considered the role that white matter connectivity plays in empathic functioning.

The aim of this thesis was to utilise a mixed methods approach, to investigate the neurocognitive networks underpinning the two major cognitive components of empathy, together with the behavioural consequences of their disruption. Firstly, DWI was utilised to investigate the relationship between white matter microstructure and the posited components of empathic functioning. Secondly, cognitive and behavioural change in bvFTD was considered, to explore the functional consequences of perturbation to these neurocognitive systems.

Across this thesis, bvFTD was considered as a model of network-based social and empathic degeneration. This approach is consistent with repeated suggestions that the study of neurodegeneration, and bvFTD in particular, may inform our understanding of the neural basis of empathic cognition (Elamin et al., 2012; Ibanez et al., 2014; Levenson et al., 2014; Zhou et al., 2012). This is in part because bvFTD, and neurodegenerative disease more widely, may selectively target specific neurocognitive systems (Seeley et al., 2009). In the case of bvFTD this system is

implicated in social and empathic functioning (Seeley et al., 2009), and profound social and empathic alterations are seen in bvFTD (Baez et al., 2014; Bora et al., 2016; Bora et al., 2015; Henry et al., 2014; Rascovsky et al., 2011).

In the first two chapters of this thesis I used an individual differences approach to study the relationship between microstructural indices of cerebral white matter, in healthy adults, as assessed using DWI and performance on cognitive tasks sensitive to the perceptual and cognitive components of empathic cognition. White matter tracts of interest were identified via a systematic review of the published literature, presented in chapter 1, regarding white matter alterations in FTD. The tracts of interest were then selected based on existing knowledge regarding the social cognitive importance of the cortical regions between which they provide connectivity. The UF and CB were selected as key tracts of interest and were the focus of chapters 2 and 3.

In chapter 2, I presented two experiments exploring the relationship between UF microstructure and facial emotion decoding in healthy young adults. Facial emotion decoding is a posited component of perceptual empathy (Blair, 2005; Shamay-Tsoory, 2011) and the UF provides connectivity between orbitofrontal and anterior temporal regions including the amygdala (Catani et al., 2002); regions shown to respond selectively to facial expressions of emotion (Grimaldi et al., 2016; Tsao et al., 2008). The experiments presented in chapter 2 showed the presence of an association between the white matter microstructure of the right UF and performance on both emotion labelling and emotion perception (oddity discrimination) tasks. No association was observed, however, with an identity oddity task and UF microstructure, showing that the observed relationships were not generalizable to face perception more broadly. Bayesian analyses further supported evidence for a selective association between right UF microstructure and facial expression decoding.

In Chapter 3, I investigated the relationship between the microstructural properties of the CB, a multi-component white matter tract (Heilbronner & Haber, 2014; Jones, Christiansen, et al., 2013), one of the brain's main limbic pathways (Catani et al., 2013), which provides connectivity between cortical regions shown to be involved in the ability to make inferences about the mental states (including emotional states) of others (Frith & Frith, 2003; Saxe & Kanwisher, 2003; Spunt & Adolphs, 2014; Yoshida et al., 2010). Often referred to as mentalising, and thought to be based on

a theory of mind, the ability to make inferences about the mental state of others is generally agreed to be virtually synonymous with cognitive empathy (Blair, 2005; Shamay-Tsoory, 2011; Shamay-Tsoory et al., 2009; Zaki & Ochsner, 2012). The results of chapter 3 showed that white matter microstructure of the left subgenual CB is related to individual differences on a novel assessment of story-based mentalising, but not on a control narrative comprehension task. Given this finding, additional supplementary analyses were run to determine the correlational double dissociation between white matter bundles and the distinct empathy tasks. In support of the posited separation of the neurocognitive networks underpinning perceptual and cognitive components of empathy, I provided statistical evidence for such a double dissociation between the right UF (related to facial emotion decoding but not mentalising) and the left subgenual CB (related to mentalising but not facial emotion decoding). This striking dissociation is strong evidence for the posited separation of neural networks underpinning affective and cognitive empathy and consistent with existing models of neurocognitive systems involved in social cognition (Bickart et al., 2014) (See figure 6.1).

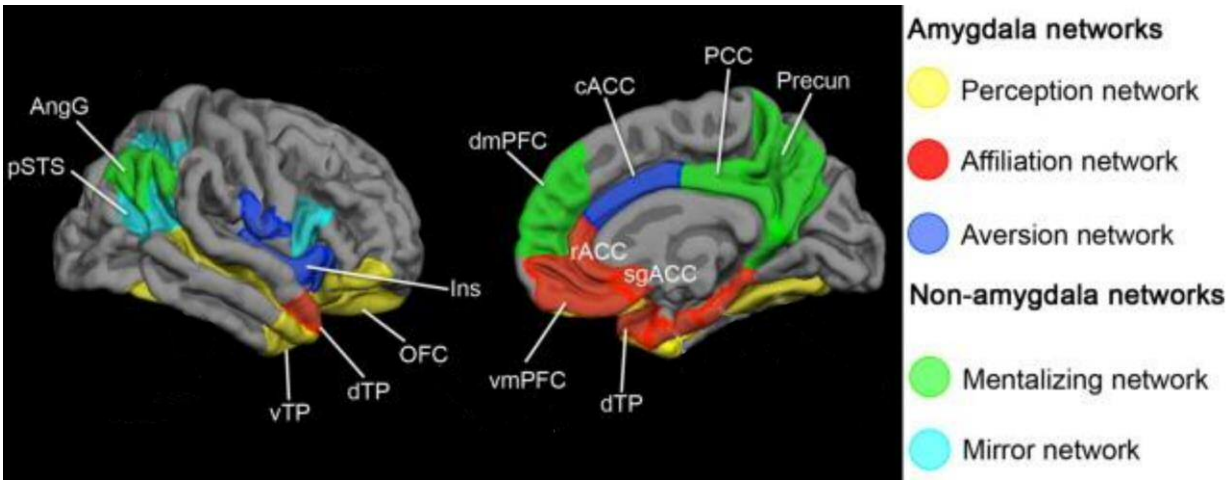

Figure 6.1. Five large-scale social neurocognitive networks. AngG=angular gyrus (temporoparietal junction (TPJ)); pSTS=posterior cingulate cortex; vTP=ventral temporal pole; dTP=dorsal temporal pole; OFC=orbitofrontal cortex; Ins=Insula; dmPFC=dorsomedial prefrontal cortex; vmPFC=ventromedial prefrontal cortex; sgACC=subgenual anterior cingulate cortex; rACC=rostral anterior cingulate cortex; cACC=caudal anterior cingulate cortex, pCC=posterior cingulate cortex; Precun= precuneus. *Adapted from Bickart et al 2014*

In chapters 4 and 5, I considered bvFTD as a model neurodegenerative disease to consider the cognitive and behavioural consequences of perturbations to the neurocognitive networks underlying empathic functioning. In chapter 4, I presented a single case study of a high functioning individual with bvFTD. This individual completed the tasks utilised in chapters 2 and 3, his performance on each provided evidence for the dissociation of cognitive and perceptual components of empathetic functioning and highlighted the potential utility of novel, ecologically valid, text-based story tasks in the detection of bvFTD. To further explore the consequences of changes to neurocognitive systems implicated in empathic cognition, in chapter 5 I presented a richly detailed qualitative description of social behavioural changes in FTD from the perspective of close family members. I discussed how the themes that emerged, in particular a change in conflicts, humour, and deception, highlight an apparent prominence of impairments in mentalising, particularly in the early stages of bvFTD.

The findings from this thesis, which utilises a novel approach to the study of empathic functioning, make several novel, substantive and valuable contributions to the existing literature. They further indicate a number of avenues for future work, exploration of which may be fruitful for not only developing our understanding of empathic functioning and its neurocognitive underpinnings but also our understanding of bvFTD. In this discussion I will detail and explore these contributions and future directions and outline a number of ways in which the results of this thesis may guide the future development of cognitive assessments that may aid in the detection and diagnosis of bvFTD.

6.2 Strengths and Implications: chapters 2 and 3

The findings of chapters 2 and 3 make a valuable contribution to our understanding of the role that white matter microstructure plays in mediating key aspects of empathic functioning. They go beyond existing lesion work, showing lower levels of self-report empathy in individuals with anterior CB and UF lesions (Oishi et al., 2015) and show that the microstructural properties of these two key white matter tracts are related to individual differences in performance on distinct empathy related cognitive tasks, even in healthy young adults. The observation of a correlational double dissociation between these tracts and tasks further provides support for the existence of two separable neurocognitive systems underlying empathy and social cognitive functioning more

generally (Blair, 2005, 2008; Decety, 2011; Decety & Jackson, 2004; Sabbagh, 2004; Shamay-Tsoory, 2011; Shamay-Tsoory et al., 2009; Tager-Flusberg & Sullivan, 2000). The selection of the UF and CB due to their early alteration in bvFTD, further means that these findings have implications for our understanding of social change in bvFTD. The associations shown in chapters 2 and 3 are consistent with the co-occurrence of early degeneration of both these structures (Agosta, Scola, et al., 2012; Mahoney et al., 2014; Santillo, Mårtensson, et al., 2013) and their associated functions (Baez et al., 2014; Couto et al., 2013; Gregory et al., 2002; Henry et al., 2014) in bvFTD. The associations observed here support the proposal that the structural change that occurs in these white matter pathways in bvFTD may have a causal role in the early behavioural symptoms of bvFTD.

The reliability and hence value of the findings of chapters 2 and 3 are supported by particular strengths of the methods used in this thesis. For neuroimaging work, the experiments reported within these chapters include large sample sizes, and as indicated by the relevant Bayes Factors, have strong evidential value. Further, in chapter 2 I present two experiments, which show a replicable relationship between UF microstructure and facial emotion decoding on the RMET, as well as convergent evidence across two different experimental tasks of emotion decoding (oddity discrimination and RMET) for this relationship. In addition, I used control tasks well matched to the tasks of interest in each chapter. Methodologically, both chapters 2 and 3 utilised native-space tractography combined with advanced DWI methods, including HARDI and CSD. This means that more biologically plausible tracts were extracted and analysed here than those which would be obtained if using standard diffusion tensor imaging methods (Hosey et al., 2005). The use of compartmental methods for the reduction of the impact of free water on diffusion metrics further enhanced the specificity of the measures of fractional anisotropy (FA) for the pathways of interest, making them more accurate representations of the diffusion qualities of the tissue within the tracts (Pasternak et al., 2009).

6.3 Strengths and Implications: chapters 4 and 5

Chapters 4 and 5 provide a valuable description of cognitive and behavioural change in the early stages of bvFTD. These chapters provide a new, more naturalistic, perspective than currently present in the majority of the literature.

In chapter 4, a novel, sensitive assessment of mentalising was utilised to assess mentalising in one high functioning individual with bvFTD. Though mentalising or cognitive empathy has been highlighted as a domain of substantial impairment in bvFTD there are issues with many existing tasks which were originally developed for use in children and lack ecological validity, particularly when used with adults (Apperly, 2013; Dodell-Feder et al., 2013). Such tasks were often developed to assess the *presence* of an understanding that others have a mental state, not the ability to accurately understand the *nature* of that mental state (Gopnik & Astington, 1988; Perner & Wimmer, 1985; Premack & Woodruff, 1978; Wimmer & Perner, 1983). As such it is of little surprise that these tests show little variability in healthy adults (Dodell-Feder et al., 2014; Duval et al., 2012; Freedman et al., 2013) and may be insensitive to subtle impairment in mentalising. Chapter 4 shows the sensitivity to bvFTD of an ecological valid, age-appropriate assessment of mental state inference, based on narrative fiction reading. The generally high level of functioning shown by the participant in chapter 4 and the large variation in performance on the SST shown across healthy adults seen in chapter 3, suggests that such assessments may have the potential to detect subtle changes in mentalising present at even the very earliest stages of disease progression. Indeed, it is feasible that such a task may be sensitive to changes in, for example, those at high genetic risk of FTD, which would open up new avenues for early detection and intervention.

The particular strength of chapter 5 was again its naturalism. While standardised assessments of social cognitive functioning requires some level of *a priori* assumption about the domains of interest, the qualitative, inductive method utilised in chapter 5 (thematic analysis of caregiver narratives) allowed for a hypothesis-free exploration of social behavioural change. This explorative approach led to the identification of three themes that, thus far, have been relatively unexplored within the bvFTD literature, if not be entirely un-noted (e.g. Clark, Nicholas, Gordon, et al., 2015; Clark, Nicholas, Henley, et al., 2015; Poletti, Borelli, & Bonuccelli, 2011; Shany-Ur et al., 2012). These themes were: changes in disagreement and conflict resolution; altered humour (particularly

the social sharing of jokes); changes to lying and deceptive behaviour. The prominence of these themes across interviews suggests that they are salient behaviour changes for family members of individuals with FTD.

A strength of chapter 5 is the potential that the findings of the chapter have to be the basis for the development of new quantitative measurements and assessment tools. The prominence of the highlighted themes suggests that these behaviour changes may be sensitive early markers of the presence of bvFTD and this means that the identified themes provide a valuable route through which we may develop sensitive neuropsychological assessments for the detection of bvFTD. This may be of great clinical utility given the challenges of assessing social cognitive change in bvFTD (Mendez et al., 2013; Mendez et al., 2007). Further to this, the systematic consideration of domains of behaviour change allowed for the theoretical consideration (in line with the grounded theory approach) of cognitive functions that may be common to the identified behaviours and underpin the observed changes. Here, this led to the discussion, in the context of knowledge of social cognitive development, of the potential role that impaired everyday mentalising may have in underpinning behavioural change in bvFTD.

Chapter 5 particularly highlights the value of including the perspectives of knowledgeable family members in research work. Chapter 5 not only describes behaviours of potential value for diagnosis and theory but also those that are of particular relevance to family members. The emergence of deceptive behaviour and difficulties in resolving conflict were particularly raised as being challenging for family members. The work of chapter 5 may thus provides a basis for further consideration of the how and why the social cognitive dysfunction that occurs in bvFTD may affect others and could provide the groundwork for the development of targeted interventions to aid families faced with bvFTD, as well as new measures of disease-specific caregiver burden.

6.4 Findings as a whole: Bringing the chapters together

Taken together, my findings show the value of mixed methods research and support the proposal that progress can be made by considering neurodegenerative diseases as a clinical model for investigating social cognitive functioning (Ibanez et al., 2014; Lawrence et al., 1998; Levenson et

al., 2014). Considered as a whole, the findings of this thesis provide further insight into bvFTD and empathic cognition beyond the results of the chapters taken in isolation.

6.4.1 Parallels between development and degeneration?

Across this thesis, and in particular in the patient work, there emerged an apparent 'last in, first out' (Raz, 2001) pattern to results. ‘Last in, first out’ refers to a pattern of change whereby those functions or structures that are latest to develop are also those that are earliest to alter in aging and degeneration. This pattern of neurodegeneration was proposed based on the observation that the pattern of brain ageing suggests that phylogenetically and ontogenetically later developing brain structures, especially association cortices, particularly the orbitofrontal cortex, dorsolateral prefrontal cortex and inferior temporal lobes, are particularly impacted by age and vulnerable to degeneration (Raz, 2001; Reisberg et al., 2002), sometimes termed ‘retrogenesis’ (Reisberg et al., 2002).

A retrogenesis-like pattern of change, whereby neurodegeneration appears to mirror development, is indicated firstly in the work reported in chapter 5. Here, reports were replete with descriptions of individuals with bvFTD showing a perceived developmental reversal: individuals with bvFTD were described by their family members as child-like or using child relevant language. This fits with previous descriptions of a last-in first-out or retrogenesis-like narrative of ageing (Reisberg et al., 2002). Consideration of the behaviours described in this way indicated that such perceived childishness may relate to a loss of relatively later developing cognitive abilities, namely more advanced mentalising abilities.

A prominent change in mentalising, in the face of relatively intact facial emotion perception, in bvFTD was shown in chapter 4. Consistent with a last-in first-out pattern of change, cognitive empathy and mentalising develop throughout childhood (Apperly, Warren, Andrews, Grant, & Todd, 2011; Blakemore, 2008; Farrant et al., 2012). While even three-year old children may spontaneously help others (Warneken & Tomasello, 2009) and consider the intentions of others when planning their own behaviour (Vaish, Carpenter, & Tomasello, 2010), there is evidence of maturational differences in mentalising and brain responsivity to the distress of others into adulthood (Decety, 2010). Perceptual empathy however appears to develop early, phylogenetically and ontogenetically. New-born human babies cry in response to the distressed

cries of others (Dondi, Simion, & Caltran, 1999), such distress in response to the distress of others is similarly seen in many non-human animals, including rodents (Bartal et al., 2011; Church, 1959; Masserman et al., 1964). Although there is evidence that perceptual empathy does improve across development (Blakemore, 2008; Rice, Anderson, Velnoskey, Thompson, & Redcay, 2016), its earlier occurrence may account for a greater endurance relative to cognitive empathy.

This last-in first-out pattern links well with the work in chapters 2 and 3, despite the fact that these chapters do not directly consider neurodevelopment or degeneration. Both the UF and the CB, are both relatively late maturing tracts (Lebel & Beaulieu, 2011)(See Figure 6.1) and, as highlighted in the introduction, show prominent alteration in bvFTD. Linking the neural and behavioural findings within the thesis, the relationship between microstructural properties of the subgenual CB and mentalising reported in chapter 3 fit neatly with the late development of mentalising and the late development of the CB (Lebel et al., 2012)(see Figure 6.2). In a retrogenesis-like account, this additionally fits with the early change in the CB and the prominent change in mentalising seen in bvFTD. Moving beyond this, CB alteration fits with a retrogenesis-like account of bvFTD as it has been shown to be the last white matter tract to mature (Lebel et al., 2012) and its alteration has

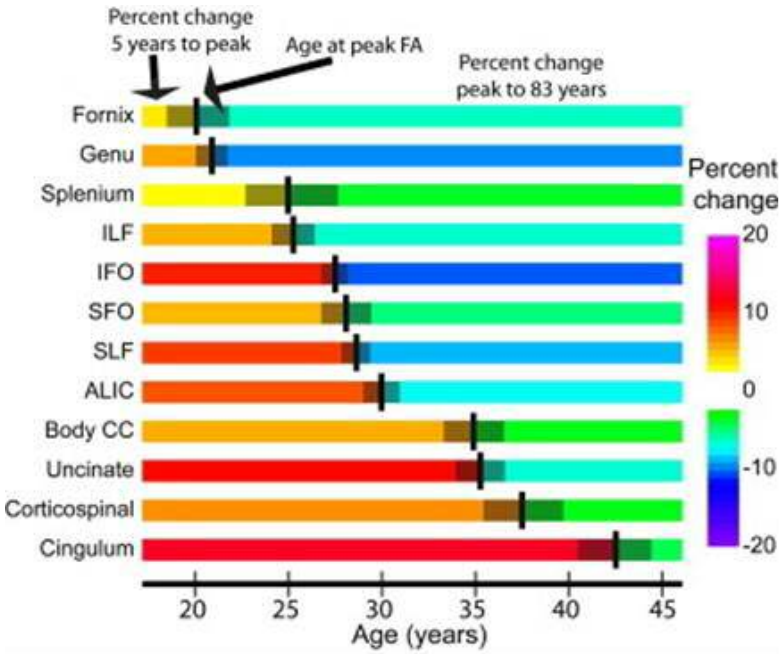

Figure 6.2. Change in Fractional Anisotropy over the maturation of cerebral white matter tracts. Black lines represent peak values and grey bars represent standard error. ILF=Inferior longitudinal fasciculus, IFO= Inferior fronto-occipital fasciculus, SFO= Superior Fronto-occipital fasciculus, SLF = Superior longitudinal fasciculus, ALIC = Anterior limb of the internal capsule, CC= Corpus callosum. *Adapted from Lebel et al 2012*

been described as a hallmark of FTD (Lillo, Mioshi, Burrell, et al., 2012). The findings of chapter 3 would then suggest that this prominent and early CB alteration in bvFTD underlies the prominent changes in mentalising reported in chapters 4 and 5.

What may lead to this selective vulnerability of the CB? One possibility, as I discussed in chapter 3, is that VEN are relatively selectively found in the CB (Nimchinsky et al., 1995) and show apparently selective degeneration in the early stages of bvFTD (Kim et al., 2012; Santillo, Nilsson, et al., 2013; Seeley et al., 2006). The reason for this selective vulnerability of VEN remains unclear, though one proposal is that VEN may selectively degenerate in FTD as their large size may lead them to have greater homeostatic demands and thus greater susceptibility to dysfunction (Schofield et al., 2003; Santillo & Englund, 2014). These neurones are highly associated with complex social behaviour (Butti et al., 2013; Santos et al., 2011) and though VEN have not, to my knowledge, been directly associated with mentalising, their location in the CB suggests that a critical role in mentalising is feasible. If true, this would have profound implications for not only bvFTD but also for our understanding of species such as elephants, whales and chimpanzees, all of whom have VEN (Butti et al., 2009; Hakeem et al., 2009; Hof & Van der Gucht, 2007). Such a link between VEN and mentalising would profoundly challenge the claim that some have made, that understanding the minds of others is a uniquely human ability (Saxe, 2006).

One challenge to the proposal of a first-in last-out pattern of change in bvFTD is the observation in Lebel et al's (2012) work that the second-to-last white matter pathway to mature is the CST. Showing maturation after the UF. On this, two brief points are worthy of note here. Firstly, several diffusion studies presented in the systematic review in the introduction did indeed identify the CST as a pathway of alteration in FTD (Lillo, Mioshi, Burrell, et al., 2012; Mahoney et al., 2014), indeed it may alter early on in FTD as it was seen to be altered in apparently asymptomatic individuals at high genetic risk for FTD (Pievani et al 2014). The absence of prominent motor symptoms would then appear to be an issue. Secondly, while the behavioural symptoms that are prominent in bvFTD are not consistent with the accepted motor role of the CST, it is worthy of note that FTLD pathology also leads to the prominently motor conditions of corticobasal degeneration, amyotrophic lateral sclerosis and progressive supranuclear palsy (Beck et al., 2008; Hsiung et al., 2012; Josephs et al., 2006; Neumann et al., 2006; Rohrer et al., 2011). This indicates that FTLD pathology does indeed appear to disproportionately target late maturing white matter. What does however remain unclear, is why some individuals, with the same pathology, show prominent CB

alteration and mentalising change, while others experience CST degeneration and motor impairment. As a possible consideration, neither condition is 'pure', and alteration to both pathways may be present in both groups, though to different degrees. Further consideration of selective vulnerability is clearly important for the understanding of conditions underpinned by FTLD.

6.4.2 Last in first out – Future directions

Supporting previous proposals that research should consider the similarities between degeneration and development (Tamnes et al., 2013), the findings of this thesis indicate that the future investigation of the posited last-in first-out pattern of change in bvFTD may be fruitful. This pattern of change suggests that FTD may show similar characteristics to developmental disorders suggesting that the simultaneous consideration of neurodevelopment and neurodegeneration may have the potential to develop our understanding of the brain and cognition, similarly to how neuropathology and psychopathology have been suggested to be able to inform one another (Elamin et al., 2012; Ibanez et al., 2014; Levenson et al., 2014; Zhou et al., 2012).

The identification of convergent findings from development and degeneration may be highly valuable as they would provide strong evidence of convergent validity for conclusions drawn about the cognitive and neural structure of social cognition. Associating perturbation of a neural system with cognitive changes can allow causal links to be made, however when many alterations occur simultaneously, such as in bvFTD, errors may be made in associations as alterations may co-vary. One way to overcome this is to look at multiple mechanisms that may cause alteration to the function of interest. In this case, as when two separate mechanisms of perturbation result in the same outcome the identifying of common sites of change gives strength to the proposal that these sites are the source of the behavioural change. On this point, it is worthy of note that prominent proposals of the sub-division of social-cognitive and empathic functioning came from the developmental literature (Blair, 2005, 2008; Tager-Flusberg & Sullivan, 2000) and are here supported by evidence from neurodegeneration.

6.4.3 ASD and FTD – Future directions

A developmental condition that may have value for consideration alongside bvFTD is autism spectrum disorder (ASD). ASD may be of value considered alongside bvFTD because of potentially overlapping social and non-social features (Mendez, Shapira, & Miller, 2005).

Functional overlap between bvFTD and ASD is most notable in the social cognitive domain. ASD is a neurodevelopmental condition defined by behavioural features including impairments in social interaction, communication and restricted and repetitive patterns of behaviour (APA 2013). Many of the assessments that have been used to show functional alteration in social cognition in bvFTD, such as the RMET and Faux-pas test, were initially developed for the assessment of ASD (Baron-Cohen et al., 1997; Baron-Cohen, O'Riordan, Jones, Stone, & Plainsted, 1999). Consistent with the focus of this thesis, a dissociation between cognitive and affective functioning with greater impairment in cognitive empathy is seen in ASD (Rogers et al., 2007; Smith 2009; Dizobek et al, 2007). Indeed it was in the consideration of ASD that some initial proposals for the seperability of cognitive and affective components of empathy were made (Blair, 2005, 2008).

It is interesting to note that within the qualitative interviews reported in chapter 5 several individuals mentioned that they felt that, from their lay understanding, their partner seemed to be developing ASD. Consistent with this, a number of the behavioural changes described by these individuals, beyond mentalising changes were notably similar to those present in ASD, such as the development of fixed and intense interest in specific domains or agitation at changes in routine. Consistent with this, one previous study showed that three individuals who showed symptoms of bvFTD, also demonstrated signs of ASD (Midorikawa & Kawamura, 2012). There has however been little to no consideration of such symptom comorbidity and, to make such consideration more challenging, we know relatively little about the behavioural symptomology of ASD in older adults (Piven & Rabins, 2011). As such the behaviours of the individuals reported here and in previous work (Midorikawa & Kawamura, 2012) are not comparable in terms of life stage or age with most descriptions of individuals with ASD. It would therefore be of value both to the understanding of ASD and of bvFTD to study the behavioural characteristics of older adults with ASD and compare these to behaviours of individuals with bvFTD of a similar age.

Considering neurodevelopment and neurodegeneration together may inform our understanding of the brain in profound ways. Beyond the similarities in altered mentalising seen between the two groups, there may be broader overlap between ASD and FTD. While there has been some discussion of functional similarities between ASD and bvFTD (Midorikawa & Kawamura, 2012), little work has been carried out to explore this relationship beyond showing that stereotypical movements, characteristic of ASD, are present in bvFTD (Mendez et al., 2005).

Future work should establish the range of non-social features of autism that are present in individuals with frontotemporal dementia. If we can indeed see that these changes are differentially present in individuals with bvFTD as compared to individuals with other neurodegenerative diseases or if these symptoms correlate with the social changes in bvFTD. If they do then this could indicate that these social and non-social behaviours could be intrinsically linked, neurally or cognitively. The first step in addressing this question would be to identify whether autistic characteristics are indeed found in bvFTD and are qualitatively similar to those seen in ASD, and whether these symptoms are correlated with social change.

Several of the structural alterations seen in bvFTD have also been proposed to be present in ASD, such as white matter change to the UF and CB (Ameis & Catani, 2015; Ikuta et al., 2014; Olson, Heide, Alm, & Vyas, 2015; Samson et al., 2016), altered functional connectivity between default network hubs (Anderson et al., 2011; Assaf et al., 2010; Weng et al., 2010; Ypma et al., 2016) and VEN abnormality (Allman et al., 2005; Santos et al., 2011). Though there is ongoing debate regarding the presence of structural alterations in ASD (Kirkovski, Enticott, Maller, Rossell, & Fitzgerald, 2015), the presence of any alterations may provide further validation for the importance of identified structures in social cognitive functioning. For example, the observation of altered CB connectivity (Ameis & Catani, 2015) and development (Cummings, 2015) in ASD is consistent with a key role for the CB in mentalising. Future research should aim to establish the nature and extent of similarity and overlap between neural and cognitive features of ASD and bvFTD.

A final valuable avenue for future work would be to establish whether, consistent with a selective vulnerability account (Mattsson, Schott, Hardy, Turner, & Zetterberg, 2016), there may be a relationship between the presence of ASD and later development of bvFTD. Initial work has suggested for example that higher rates of dyslexia and dyslexia-associated genes are present in

individuals with the PPA variant of FTD (Paternico et al., 2015; Rogalski, Johnson, Weintraub, & Mesulam, 2008). It is feasible that in the same way, higher rates of ASD or ASD associated genes could be present in individuals with bvFTD. Such work would however require a large-scale, longitudinal study. Yet, developing such understanding may be mutually beneficial to these fields as the study of the neural regions that show alteration in FTD could inform our investigation of brain changes in autism, while the understanding and methods for assessing the cognitive symptoms of autism could further inform assessment and investigation of the cognitive and non-cognitive symptoms of frontotemporal dementia.

6.5 Clinical implications and utility

6.5.1 Developments in understanding cognitive functioning for FTD assessments

The study of FTD for understanding social cognition may have reciprocal benefits for FTD, as improving understanding of the cognitive underpinnings of social cognition may aid in the development of targeted assessments that are sensitive to early changes in FTD.

Early diagnosis of neurodegeneration is a key goal for science and medicine. Firstly, because treatments for neurodegeneration are likely to only delay or prevent the progress of neurodegeneration, early intervention will be necessary to minimise cognitive and neural damage. Secondly, in the case of bvFTD early diagnosis is of importance because bvFTD can have a huge social impact on affected individuals and those close to them. Changes in socially important skills such as judgement, social understanding, tact, self-awareness, inhibition and decision making can lead to job loss, relationship breakdown, financial difficulties and in over a third of those diagnosed with bvFTD, criminal behaviour such as theft, sexual advances, trespass, public urination and traffic violation (Liljegren et al., 2015; Mendez, 2010). Early diagnosis can provide an explanation for symptoms and allow family members to adapt to their new roles as caregivers and allow them to plan for future care arrangements (de Vugt & Verhey, 2013).

6.5.2 Functional change

The work presented here may be of potential clinical value as it could help to guide the development or refinement of clinical assessments for the early detection of bvFTD. The potential centrality of changes to mentalising was highlighted in chapter 5 and the findings of chapter 4 highlight the potential utility of text-based story tasks for the assessment of early cognitive changes in bvFTD. These findings could be extended to non-language forms of narrative, for example movies, to enable assessments in individuals with less well-developed or impaired language skills. Chapter 5 further highlighted the potential utility of humour and comprehension of figurative speech in particular as domains that may have sensitivity to early changes in bvFTD. There has been a limited consideration of humour in bvFTD (Clark et al., 2016; Clark, Nicholas, Henley, et al., 2015), and consistent with the results reported here, previous reports describe increased fatuous and childlike humour in individuals with bvFTD (Clark et al., 2016). Regarding the comprehension of figurative speech, there is some literature regarding sarcasm comprehension. The Awareness of Social Inference Test (TASIT)(McDonald et al., 2003) is a 3-part assessment used in bvFTD in which part 2 requires participants to distinguish sincere and sarcastic speech and part 3 requires the distinguishing of sincere, sarcastic and deceptive speech. Several papers have reported impaired sarcasm comprehension in bvFTD using the TASIT (Kipps et al., 2009; Kumfor et al., 2017; Kumfor et al., 2014; Rankin et al., 2009). Indeed, consistent with the findings here, impairment on the sarcasm components of the TASIT have been shown to be more prominent than face based emotion recognition impairments (Kumfor et al., 2017). The work here would suggest that extension of these assessments of humour and sarcasm would be potentially fruitful for improving early detection of bvFTD, as may extension of the assessment of deceptive speech.

6.6 Limitations

6.6.1 Executive functioning

As touched on previously, a limitation of the work and some of the conclusions drawn from this thesis is the relatively sparse consideration of wider cognitive functions that may influence empathic functioning. Executive functioning in particular has been discussed as a vital component

of empathy (Decety & Jackson, 2004; Decety & Lamm, 2006). It is impaired in bvFTD across a range of tasks (Collette et al., 2007; Possin et al., 2013), although evidence for a relationship between executive dysfunction and empathy change in bvFTD has been mixed (Eslinger et al., 2007; Gregory et al., 2002; Lough et al., 2001; Lough & Hodges, 2002; Lough et al., 2006; Snowden et al., 2003; Torralva et al., 2007). Executive function was not explicitly studied either with cognitive assessments or in qualitative discussions with families. Yet, it is feasible that executive functioning may influence some of the findings relating to cognitive empathy given here. A role for executive functioning in the alterations in cognitive empathy seen in chapters 4 and 5 is plausible. Particularly with regards to the qualitative exploration of social behaviour, it is not feasible to draw strong conclusions about what functional domain(s) underlies the behaviours observed. Yet, such clear distinctions between functions are not the principal goals of such qualitative, descriptive work and thus do not pose an issue for the work reported here. That said, the literature would benefit from further work to disentangle these key functions and their impact on behaviour in bvFTD. Future work should additionally utilise larger batteries of tasks, including executive tasks to disentangle the relationship between CB structure, empathic function, mentalising and executive abilities.

6.6.2 Lateralization of function

In both chapters 2 and 3, the relationships between white matter microstructure and individual differences in cognitive task performance were lateralised. In chapter 2 UF microstructure was only seen to be related to facial emotion processing in the RH while in chapter 3 mental state inference was related to the microstructural properties of the subgenual CB in only the LH. As discussed in the relevant chapters, these findings are consistent with other work showing a RH specialization for face processing, and a LH specialization for language. Though these relationships were seen to be significantly greater than those in the opposing hemispheres, the absence of a relationship between the microstructure of a pathway and a task is not necessary evidence that the pathway is not involved in the task, and any lateralization is likely to be partial or graded rather than absolute.

Regarding the UF, recent tractography studies have shown that the UF may be distinguishable into multiple components, several of which show lateralisation (Hau et al., 2016). Of the sub-

components of the UF, those connecting OFC & TP show a right lateralisation of volume (Hau et al., 2016), consistent with greater connectivity being reported between OFC and ATL in the RH than the LH (Binney et al., 2012; Papinutto et al., 2016). As such, fibres connecting the OFC and ATL may have a greater influence on total tract FA in the RH than the LH, as facial emotion processing is argued to involve the OFC and ATL (Rolls, 2015; Rutishauser, Mamelak, & Adolphs, 2015; Tsao et al., 2008). This greater influence of these fibres in the RH may drive the presence of a significant relationship between tract FA and task performance, but it does not mean that these fibres in the LH do not have the same or a similar role, merely that they exert less overall influence on the average FA when measured across the whole tract.

6.6.3 Mixed methods

There was considerable value in the combination of multiple research methods in a single thesis, however, this mixed-methods approach did not come without its challenges, as discussed in chapter 5. A fundamental issue with mixed methods work is that it can present issues of dealing with disciplines with differing epistemologies. It is inescapable that the work presented here is the work of a researcher with a background in experimental cognitive psychology. While the qualitative work presented here utilises methods and approaches rooted in the social sciences, it diverges from the approach that many within these fields take, as there is still an expectation of producing results that may be extendable and lead to future generalisations across individuals not included in this work (although this is compatible with some approaches to grounded theory (Charmaz, 2006)). Further interdisciplinary work and collaboration is necessary to develop understanding of how best to approach such epistemological differences. The work presented here should be viewed as a step towards an approach that may allow for disciplines to collaborate and move forwards to address important questions about social cognitive functioning.

6.6.4 On ‘Empathy’

As outlined in the introduction to this thesis, there remains little agreement on the definition of empathy and this is in part due to different definitions being given depending on the background, research questions, method and approach of a researcher and paper. Though I acknowledged the variability in definitions of empathy, I have continued to use the term ‘empathy’ throughout,

despite proposals from leading researchers in the field that it may be advisable to move beyond this term (Decety & Cowell, 2014; Decety, Smith, Norman, & Halpern, 2014). As such it is a reasonable critique of this work that it lacks some specificity in some of its terminology. Cognitive, affective and perceptual empathy all remain broad terms, despite my attempts to provide greater clarity. This is however an issue for the field in general and a challenge to be addressed by the field as a whole. To move forwards, greater consistency is necessary in how researchers interested in social cognitive functioning describe and operationalize different domains, including empathy, emotion decoding, theory of mind, mentalising and sympathy. Inconsistency in definition means that, currently, tasks that claim to tap the same function assess wildly different functions, such as in the case of mentalising/theory of mind (Achim et al., 2013; Schaafsma et al., 2015; Schurz et al., 2014). It surely would be desirable for researchers to come to a common agreement of the meaning of terms (a shared "cognitive ontology") such that results from tasks and studies claiming to address the same cognitive function are indeed comparable.

It is my belief, on the back of this thesis that, as recommended by Decety (Decety & Cowell, 2014; Decety, Smith, Norman, & Halpern, 2014), it would be desirable for the field to move beyond the use of the term 'Empathy'. Instead, the field should consider empathy in terms of its constituent components, in line with existing models of the cognitive and neural structure of empathy. The results of this thesis provide strong evidence for the need for such a separation by providing strong evidence for the dissociability of two key components of empathy, namely cognitive and perceptual empathy. By showing a double dissociation in the white matter pathways that show a relationship with each cognitive function and a dissociation in the impairment on these functions in one patient diagnosed with bvFTD this work emphasises the distinction of these components and importance of not conflating them.

The work of this thesis, in the context of existing work, strongly suggests that empathy is not only comprised of separable components but also that perturbation of the networks that support these components may result in distinct behavioural consequences. Thus, rather than empathy change being a single thing, there may be many different behavioural consequences of changes to the separate networks that underpin empathic functioning. The evidence from this work indicates that the perceptual component of empathy involves frontal and temporal regions, the intercommunication of which is underpinned in part by the UF. While the behavioural consequences of alteration to this system were not explored in detail here it seems feasible that

impairment to the perceptual components of empathy will result in limited awareness of the emotion of others. If unable to detect emotional signals then an individual may be less sensitive to the emotional state of others and many act uncaringly due to a limited awareness of emotional state. This interestingly does fit with some of the behaviour of individuals with bvFTD who can appear insensitive to others who are expressing intense emotion, such as crying.

The evidence from this work indicates that the cognitive component of empathy, which can alternatively be described as the affective component of mentalising or theory of mind, is underpinned by a network of regions that at least in part sit along the cortical midline and are supported by anterior portions of the cingulum bundle such as the sub-genual CB. This is consistent with existing models of the neural underpinnings of affective mentalising (Abu-Akel & Shamay-Tsoory 2011). The behavioural consequences of changes to this system may be many and complex but this thesis presented an initial exploration of behavioural changes that may be partly due to changes in the ability to mentalise. Here alterations in conflict resolution, sense of humour and apparent deception were discussed as potential behavioural consequences of changes to mentalising that may result as a consequence of FTD. Changes in mentalisng may result in changes to such complex interpersonal behaviours due to impairment in the ability to flexibly consider the intentions and perspectives of others. This is a new perspective on cognitive empathy, made possible through the use of mixed methods research and in particular qualitative research methods draws in a wider range of behaviours than are often considered in relation to empathy but such an approach may help with the development of a more accurate understanding of empathic functioning. Indeed characteristic such as sense of humour provide a novel insight into empathic functioning and allow for a consideration of shared emotion that goes beyond understanding of negative emotion, which tends to be the focus of classical considerations of ‘empathy’.

6.7 Future directions - methodological elaboration

This thesis established the presence of associations between two aspects of empathy (emotion decoding, mentalising) and distinct white matter pathways (UF, CB). Future work should clarify and elaborate on the relationships outlined here by utilising more extensive cognitive batteries with a greater scope to increase the specificity of the relationships described. Such work would

additionally benefit from using more advanced imaging protocols and analysis methods which may allow for the estimation of more biologically specific metrics of tracts such as axonal diameter (De Santis et al., 2014; Assaf et al., 2008; Sepehrband et al., 2016). Regarding the UF, future batteries should include stimuli from multiple modalities, such as auditory emotional stimuli and non-facial visual stimuli, such as bodily expressions of emotion to allow for the consideration of whether the observed relationship between UF microstructure and facial emotion is face specific or emotion general. Work should further establish the extent to which emotion is related to UF microstructure due to the important role of valence or salience in emotion. According to the hub and spoke model of the ATL as a semantic hub the UF may be critical to emotion due to providing the connectivity between semantic representations in the ATL and valence-based information in the OFC (Lambon-Ralph et al., 2017; Patterson, Nestor, & Rogers, 2007).

Regarding the CB, work should further explore the relationship between CB and mentalising ability, however for this, alternative assessments to the SST, which show variability in healthy adults, need to be established. Of particular value would be assessments separating emotion related mental state inference and non-emotional cognitive state inference to establish whether the observed relationship is common to all mental states, given that cognitive and affective mental states are conflated in the SST scoring system. As mentioned earlier, film based narratives may also be useful in this context.

To increase the specificity of the associations outlined here, further sub-components of the reported tracts could be investigated to consider with greater precision the cortical regions between which connectivity is of relevance for empathic functioning. To provide further specificity functional imaging could be utilised to guide tract selection, as described in a recent investigation of the UF (Metoki, Alm, Wang, Ngo, & Olson, 2017). Here, face sensitive patches were isolated based on functional imaging work and these ROIs used as seed regions for tractography. Such work could use probabilistic as well as deterministic tractography to establish the connectivity of these face selective patches. Though Metoki et al. (2017) used established ROIs it would be preferable to run a functional localiser in each participant to allow for face selective regions to be isolated for each participant, to maximise the accuracy of the native-space tractography. Such analyses could be performed for both the UF and CB. As described above the UF may additionally be divisible into separable components, each with distinct connectivity (Hau et al., 2016). Splitting the UF into such pathways, using very high resolution imaging, could be carried out to establish

whether it is indeed the presence of greater connectivity between the ATL and OFC in the right hemisphere that drives the relationship reported in chapter 2 and to establish whether it is the sections of the UF that connect specifically to the OFC that are selectively related to facial emotion decoding.

Incorporation of functional imaging alongside diffusion imaging would allow for functional connectivity analyses to be carried out considering white matter as a mediator in connectivity between regions, consistent with methods reported in previous work (Hodgetts et al., 2015). Such work could be used to further investigate the proposal that white matter may influence cognitive functioning by facilitating neural synchronisation (Bells, Lefebvre, & Prescott, 2017).

6.8 Overview – Advantages of Mixed methods

Mixed methods research utilising imaging, patient work and qualitative methods is relatively rare, however it is my belief that a mixed methods approach has great potential value to the investigation both of social cognitive functioning and functional change in bvFTD.

The work presented here outlined how qualitative methods were used to obtain richly detailed ecologically relevant descriptions of behaviour from individuals with detailed knowledge of behavioural changes that occur as a result of structural brain changes. The consideration of this information alongside imaging and quantitative patient work provided support for a prominent mentalising deficit in bvFTD, and its salience, as it emerged through an inductive, grounded theory approach. The combination of methods further allowed for a potential explanation for why this deficit may emerge to be proposed, based on imaging evidence from healthy adults.

The apparent dissociation of mentalising and facial emotion perception, across methods, provides support for the two-stream model of empathy and the dissociation of these streams. The fact that this pattern was seen across research methods provides converging evidence for this claim.

The use of qualitative methods alongside the other methods allowed for two potentially valuable observations to be made: (a) the presence of a retrogenesis-like pattern of change and (b) a potential commonality between bvFTD and ASD. The similar pattern across methods adds strength

to the pattern of observations, indicating that it was not a characteristic of a particular research approach.

6.9 Conclusions

The aim of this thesis was to take a novel approach to the consideration of empathic functioning though the use of mixed, methods and bvFTD as a clinical model of empathic impairment due to brain network pathology. Empathic functioning has been proposed to comprise two functional 'streams' each underpinned by a network of functional neural regions (Decety & Jackson, 2004; Shamay-Tsoory, 2011; Shamay-Tsoory et al., 2009). The work presented provided novel evidence for this dissociation using DWI, single-case neuropsychology and qualitative, narrative methods.

The work in this thesis speaks to the value of both using mixed methods and of bvFTD as a model neurodegenerative disease for the study of empathic functioning. The mixed methods approach provided evidence from multiple domains of a retrogenesis-like pattern of change in bvFTD and provided evidence for the potential clinical utility of assessments of the CB and mentalising in bvFTD. This work may usefully direct future development of cognitive assessments for both empathic functioning and for the detection of bvFTD.

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