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Function and Dysfunction in Distinct Facets of Empathy

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Neuroscience

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Abstract

Empathy is crucial for successful social interactions and it is impaired in many devastating disorders. Empathy deficits are highly burdensome for affected individuals, caregivers, and significant others, and costly for society as a whole. However, empathy is thought to be a multifaceted construct, including cognitive empathy, affective sharing, and empathic concern components. These constituents may be linked to different behavioural outcomes and neurocognitive substrates, and presentation varies depending on the facets affected. Thus, there is a critical need to determine the behavioural and neurocognitive substrates of different components of empathic responding, and how these are affected in particular disorders.

The present work aimed to elucidate the nature of different components of empathy and how they vary as a function of clinical diagnoses and individual differences in subclinical traits, as well as their underlying functional neural mechanisms. Study I used the Multifaceted Empathy Test, a performance-based task tapping cognitive empathy, affective sharing, and empathic concern elicited by realistic emotional images, in patients with behavioural variant frontotemporal dementia (bvFTD). This revealed a global cognitive empathy deficit, deficient affective sharing for negative experiences, and a generalized processing impairment for negative stimuli in bvFTD. In Study II, healthy adults completed the Multifaceted Empathy Test and questionnaire measures of autistic traits, coldhearted psychopathic traits, and trait anxiety. Coldhearted traits were found to disrupt affective sharing and empathic concern, whereas trait anxiety appeared to influence subjective affective experience via generalized arousal. Study III investigated the involvement of action-perception matching, simulation mechanisms in cognitive versus emotional empathy, using fMRI during cognitive empathy, emotional empathy, and simulation network localizer tasks in healthy adults. Increased activation was observed in identified simulation regions during emotional versus cognitive empathy, providing evidence for greater involvement of simulation mechanisms in emotional empathy.

Taken together, this work suggests that cognitive empathy, and emotional empathy, including affective sharing and empathic concern, represent aspects of empathy that are

distinguishable and differentially linked with certain patient populations, subclinical traits, and neurocognitive mechanisms. These findings are discussed with respect to the nature and conceptualization of empathy and its components, as well as implications for disorders featuring empathy dysfunction.

Keywords

empathy; cognitive empathy; theory of mind; emotional empathy; affective sharing; empathic concern; emotion; frontotemporal dementia; psychopathic traits; autistic traits; trait anxiety; functional magnetic resonance imaging; mirror neuron system; simulation

Co-Authorship Statement

Chapter 1, the introduction, and Chapter 5, the general discussion, were written by Lindsay Oliver with input from Derek Mitchell and Elizabeth Finger. Chapter 2, entitled “Parsing cognitive and emotional empathy deficits for negative and positive stimuli in frontotemporal dementia,” was written by Lindsay Oliver with input from all co-authors. Isabel Dziobek was also involved in task design, Julia MacKinley and Kristy Coleman were involved in data collection, and Elizabeth Finger and Derek Mitchell were involved in experimental design and data analysis. Chapter 3, entitled “Distinguishing the relationship between different aspects of empathic responding as a function of psychopathic, autistic, and anxious traits,” was written by Lindsay Oliver with input from all co-authors. Richard Neufeld was also involved in data analysis, Isabel Dziobek was involved in task design, and Derek Mitchell was involved in experimental design. Chapter 4, entitled “The neurocognitive correlates of distinct facets of empathy: Greater involvement of simulation mechanisms in emotional relative to cognitive empathy,” was written by Lindsay Oliver with input from Derek Mitchell and Elizabeth Finger. Joana Vieira was also involved in data collection, and Derek Mitchell was involved in experimental design and data analysis.

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Chapter 1

1 Introduction

While walking through the park, you spot a man with tears in his eyes sitting under a bridge, shivering beneath a thin dirt-laden blanket. You infer that he is feeling miserable, and likely homeless. His apparent sorrow also fills you with sadness and concern for him. Later that day, your daughter's face breaks into a huge grin and she raises her fist into the air upon receiving a call about a recent job application. You sense that she is feeling excited and that she probably got the job. You swell up with excitement and feel happy for her. These reactions exemplify the phenomenological experience of empathy for both negative and positive experiences, including cognitive aspects (understanding the feelings of others) and emotional aspects (sharing or reacting affectively to the feelings of others).

Empathy is a crucial component of successfully interacting and relating with strangers and those known intimately alike, and it is impaired in many debilitating disorders. It is easy to see why empathy deficits are highly debilitating. Empathy is thought to be one important means by which we are able to respond appropriately to someone else's emotional state, and adapt our social behaviour. Accordingly, patients with empathy impairments demonstrate atypical or inappropriate social behaviour (Finger, 2016; Frith, Happe, & Siddons, 1994; Hare, 1996). However, it is important to note that empathy is thought to include several components, which may be linked to different behavioural outcomes and neurocognitive substrates, and presentation may vary depending on the facets affected. Beyond the negative impact empathy impairments have on affected individuals, they are also extremely distressing to significant others and caregivers, and costly for society as a whole (Weder, Aziz, Wilkins, & Tampi, 2007). Indeed, evidence suggests that socioemotional deficits are a source of great burden to both patients and caregivers (Boutoleau-Bretonniere, Vercelletto, Volteau, Renou, & Lamy, 2008; Diehl-Schmid et al., 2013; Hillis & Tippett, 2014; Uflacker, Edmondson, Onyike, & Appleby, 2016). With regard to societal impact, empathy has been positively associated with prosocial behaviour (Batson, 1991; Batson, Fultz, & Schoenrade, 1987; Eisenberg, Fabes, & Spinrad, 2006), whereas empathy deficits have been linked to aggressive, antisocial behaviour (Miller & Eisenberg, 1988), as well as criminal behaviour and violent offending (Eisenberg, Eggum, & Di Giunta, 2010; Jolliffe & Farrington, 2004). Consequently, treatments that focus on underlying cognitive and neurological risk factors in individuals with empathy dysfunction are essential. Elucidating

the nature of empathy and the dissociability of its constituents will also be pivotal for identifying such risk factors and providing targeted treatments for deficits in particular components of empathy. Crucially, there are currently no approved treatment options to target these devastating socioemotional impairments (Eslinger, 1998; Finger, 2011). Thus, there is a critical need to determine the behavioural and neurocognitive substrates of different components of empathic responding, and how these are affected in particular disorders.

1.1 Empathy and Its Components

The term empathy came from the translation of “Einfühlung” (Titchener, 1909), a German word meaning ‘to feel into’. Einfühlung was first used in the context of intersubjectivity by the philosopher Theodor Lipps, referring to the projection of oneself into the situation of another (Lipps, 1903). Other earlier canonical definitions of empathy include experiencing emotions more applicable to someone else’s situation rather than your own (Hoffman, 1987), or an emotional response akin to another individual’s based on understanding their affective state (Eisenberg, Shea, Carlo, & Knight, 1991). It has also been described as imagining how someone else feels by adopting their perspective (Batson, Early, & Salvarani, 1997), or projecting oneself into another’s mental shoes to simulate their feelings (Goldman, 1992). Such definitions tend to favour certain aspects of empathy. Taken together, empathy is defined here as the comprehension of, identification with, and vicarious experience elicited by another individual’s mental state. At present, empathy is largely considered to be a multidimensional construct, including both cognitive and emotional facets (Blair, 2005; Davis, 1980; Decety & Jackson, 2004; Eslinger, 1998; Shamay-Tsoory, 2011). Further, though there is variability in the purported distinct components contributing to empathy (Batson, 2009; Blair, 2005; de Vignemont & Singer, 2006; Decety & Jackson, 2004), it is widely believed to include cognitive empathy, affective sharing, and empathic concern constituents (Bernhardt & Singer, 2012; de Waal, 2008; Decety & Cowell, 2014b; Decety & Jackson, 2004; Hatfield, Rapson, & Le, 2009; Preston & de Waal, 2002; Zaki & Ochsner, 2012).

1.1.1 Cognitive empathy and its neural correlates

Cognitive empathy is often used interchangeably with theory of mind (Blair, 2005; Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004) and refers to the capacity to understand another individual's perspective, and thereby infer their emotional or mental state. Despite some variability, the core neural substrates of cognitive empathy have been fairly well-established and replicated across a variety of paradigms tapping mental state inference, including belief and intention understanding, utilizing both verbal and visual stimuli (Carrington & Bailey, 2009; Mitchell, 2009). Indeed, meta-analyses of functional magnetic resonance imaging (fMRI) studies have demonstrated that cognitive empathy consistently elicits activity in areas including the medial prefrontal cortex (mPFC), the temporoparietal junction (TPJ), the superior temporal sulcus (STS), and precuneus, and sometimes the inferior frontal gyrus (IFG) and temporal poles (Bzdok et al., 2012; Mar, 2011; Molenberghs, Johnson, Henry, & Mattingley, 2016; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014; Van Overwalle, 2009). Certain tasks that reliably recruit these core regions have also been validated and used as cognitive empathy localizers, including the False-Belief Task (Dodell-Feder, Koster-Hale, Bedny, & Saxe, 2011; Dufour et al., 2013) and the Why/How Task (Spunt & Adolphs, 2014).

Lesion data indicates that the mPFC and TPJ are particularly important for cognitive empathy. More specifically, an early lesion study demonstrated cognitive empathy deficits in individuals with lesions of the ventromedial PFC in comparison to patients with lesions outside of this region and healthy controls (Stone, Baron-Cohen, & Knight, 1998). Subsequent investigations have corroborated these findings, providing evidence for impaired cognitive empathy in patients with lesions of the mPFC (Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003; Shamay-Tsoory, Tomer, Goldsher, Berger, & Aharon-Peretz, 2004; Stuss, Gallup, & Alexander, 2001). Though fewer studies have included such patients, impaired cognitive empathy performance has also been observed in three individuals with lesions of the left TPJ (Samson, Apperly, Chiavarino, & Humphreys, 2004). Consistent with these findings, application of repetitive transcranial magnetic stimulation over the right TPJ has been found to impair performance on cognitive empathy tasks, including increased response times for false belief detection and reduced mental state attribution accuracy, as compared to control stimulation (Campanella, Shallice, Ius, Fabbro, & Skrap, 2014; Costa, Torriero, Oliveri, & Caltagirone,

2008). Thus, there is some evidence to suggest that both the mPFC and TPJ are necessary for cognitive empathy.

1.1.2 Emotional empathy and its neural correlates

Emotional empathy has been used to refer to both affective sharing and empathic concern components of empathy. Indeed, prior work often does not distinguish between these components, referring to either using this overarching construct (Decety, 2009; Vossen, Piotrowski, & Valkenburg, 2015). Affective sharing refers to the ability to share the emotional experience of another person, whereas empathic concern relates to the motivation to care for the welfare of another, including feelings of compassion and concern. Thus, affective sharing involves an emotional response that is congruent with that of another individual, while empathic concern may not. Investigations involving functional imaging of emotional empathy have identified consistent activation in areas including the anterior insula, anterior cingulate cortex, and IFG, and sometimes the dorsomedial PFC, amygdala, and inferior parietal lobule (IPL), as evidenced by reviews (Shamay-Tsoory, 2011; Walter, 2012) and meta-analyses (Bzdok et al., 2012; Fan, Duncan, de Greck, & Northoff, 2011; Lamm, Decety, & Singer, 2011). This functional imaging evidence is corroborated by findings from lesion studies. For example, reviews of focal lesion studies addressing emotional empathy have also suggested that the anterior insula and IFG are critical for emotional empathy (Hillis, 2013; Shamay-Tsoory, 2015). Of particular interest, lower questionnaire scores of emotional empathy have been associated with damage to the right insula in veterans with traumatic brain injuries (Driscoll, Dal Monte, Solomon, Krueger, & Grafman, 2012), and impaired emotional empathy for pain has also been demonstrated in individuals with anterior insula, but not anterior cingulate cortex, lesions (Gu et al., 2012).

1.1.2.1 Affective sharing versus empathic concern

Investigations regarding the neural substrates of empathy have focused primarily on neural systems involved in cognitive and emotional empathy, as opposed to parcellating affective sharing and empathic concern. This may be in part because these constructs can be difficult to

disentangle as they are concurrently elicited in many circumstances. Thus, less is known regarding the differences between neural circuitry involved in these components of empathy. However, a meta-analysis has demonstrated that affective sharing for pain is associated with activity in the anterior insula into the IFG, the anterior cingulate cortex, and the precuneus, based on common recruitment during both directly experienced pain and empathy for pain (Lamm et al., 2011). In contrast, training in empathic concern has been found to produce greater activation in the ventromedial PFC and ventral striatum to distressful social videos in comparison to memory training (Klimecki, Leiberg, Lamm, & Singer, 2013). Consistent with these findings, in a subsequent study, training healthy individuals in affective sharing increased subsequent activity in the insula, anterior cingulate cortex, and the dorsal striatum to distressful videos, whereas empathic concern training heightened activation in the ventromedial PFC, anterior cingulate cortex, and the ventral striatum (Klimecki, Leiberg, Ricard, & Singer, 2014). Thus, there is some evidence to suggest that affective sharing and empathic concern may be subserved by at least partially distinct neural systems.

Delineating these different components of emotional empathic responding is important because they may be associated with different behavioural outcomes. For example, there is evidence that empathic concern motivates prosocial behaviour and the desire to relieve the stress of another individual in distress (Batson, Duncan, Ackerman, Buckley, & Birch, 1981). In contrast, observing another in a negative situation can alternatively elicit personal distress, or feelings of anxiety and discomfort in response to another individual's distress (Davis, 1980). Personal distress has been associated with motivation to relieve one's own discomfort and stress (e.g., promoting aversion) as opposed to motivating approach and altruistic behaviours that relieve the distress of another (Batson, 1991; Batson et al., 1987; Eisenberg et al., 2006). Specifically, responding with predominantly empathic concern to the distress of another individual has been associated with offering help even when it is easy to escape the situation (i.e., altruistic responding), whereas responding to another's distress by expressing predominantly personal distress has been linked to helping less often if escape or avoidance is easy (Batson, 1991; Batson et al., 1987). Personal distress is believed by some to be a form of emotional empathy akin to emotional contagion (Dziobek et al., 2008; Rankin, Kramer, & Miller, 2005), which may align to some degree with affective sharing for negative situations (Singer & Klimecki, 2014). Therefore, these findings suggest that differences in empathic

concern are linked with prosocial and altruistic behavioural outcomes in response to the affective experience of another individual. In contrast, high affective sharing levels may be related to greater personal distress in response to negative social situations and therefore have fewer implications for motivating altruistic behaviour (Batson et al., 1987; Decety & Svetlova, 2012; Eisenberg et al., 2006).

1.1.3 Alternative conceptualizations of empathy

It is important to note that there are alternate conceptualizations of empathy and its constituents, some of which adopt different terminology (de Vignemont & Singer, 2006; Decety & Cowell, 2014a, 2014b; Singer & Lamm, 2009). Here we include affective sharing and empathic concern under the facet of emotional empathy because they both involve the elicitation of an affective response. Importantly, the nature of affective sharing and empathic concern constructs tends to remain constant, even though the nomenclature may differ.

Additionally, autonomic arousal has also long been considered integral to the experience of empathy (Ax, 1964), and emotional empathy in particular (Batson, 2009). Accordingly, emotional empathy is sometimes assessed via autonomic arousal (Blair, Jones, Clark, & Smith, 1997; de Wied, Boxtel, Posthumus, Goudena, & Matthys, 2009; Eisenberg & Fabes, 1990). However, limited research has focused on the relationship between arousal and different components of empathy. High questionnaire scores of emotional empathy in healthy individuals have been associated with increased physiological arousal (Balconi & Bortolotti, 2012a, 2012b, 2014; Bogdanov et al., 2013; Wiesenfeld, Whitman, & Malatesta, 1984) and subjective arousal ratings (de Sousa et al., 2010) in response to emotional videos and images. Interestingly, most of the questionnaire measures used in these investigations assess vicarious emotional responding, suggesting a link between autonomic arousal and questionnaire measures of emotional empathy akin to affective sharing, which may have fewer implications for prosocial behaviour. However, results are mixed (Eisenberg et al., 2006; Fabes, Eisenberg, & Eisenbud, 1993; Gu et al., 2015), with some investigations finding no significant relationship between self-reported emotional empathy scores and physiological arousal (Anastassiou-Hadjicharalambous & Warden, 2007; de Sousa et al., 2011) or subjective arousal ratings (de Sousa, McDonald, & Rushby, 2012) in response to emotional stimuli. Further, most investigations do not include behavioural indices of

different aspects of empathic responding in conjunction with autonomic measures. Thus, there is a need to elucidate the potential link between empathy and arousal, and whether autonomic arousal is indeed reflective of emotional empathy. It is also unclear whether arousal contributes to the experience of particular aspects of empathy, such as affective sharing or empathic concern.

1.1.4 Cognitive versus emotional empathy

Taken together, functional neuroimaging and lesion studies have implicated largely different neural substrates in cognitive and emotional empathy, providing evidence for their dissociability. Indeed, a lesion study has demonstrated a double dissociation between cognitive and emotional empathy, observing a cognitive empathy deficit with intact emotional empathy in patients with ventromedial prefrontal cortex lesions, and impaired emotional empathy but intact cognitive empathy in patients with lesions to the IFG (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). Further support for this double dissociation comes from behavioural data in clinical populations featuring empathy impairments (Jones, Happe, Gilbert, Burnett, & Viding, 2010; Schwenck et al., 2012), as well as some trait correlational data in the healthy population (Lockwood, Bird, Bridge, & Viding, 2013). However, it should be noted that the demonstration of a double dissociation does not preclude the possibility that cognitive and emotional empathy are related to some degree. It may be the case that these constructs are separable, but interact and often do not occur in isolation (Shamay-Tsoory et al., 2009). Accordingly, these aspects are widely believed to influence one another and both contribute to our phenomenological experience of empathy (Cox et al., 2012; Decety & Svetlova, 2012; Kerem, Fishman, & Josselson, 2001; Shamay-Tsoory, 2011). Nevertheless, the apparent dissociability of cognitive and emotional empathy is indicative of different underlying mechanisms. The conceptualization of empathy and its components presently considered is depicted in Figure 1.1.

Notably, the components of empathic responding affected in patient populations characterized by empathy impairments have been elucidated to varying degrees and remain unclear in many cases. Further, less is known in both clinical and healthy populations about the dissociability of affective sharing and empathic concern. Indeed, as mentioned, many investigations to date do not distinguish between these two putative components of empathy. From a clinical perspective, addressing these gaps in knowledge is critical because the

demonstration of a deficit in a particular aspect of empathy informs potential targeted treatment or compensatory options for affected patients.

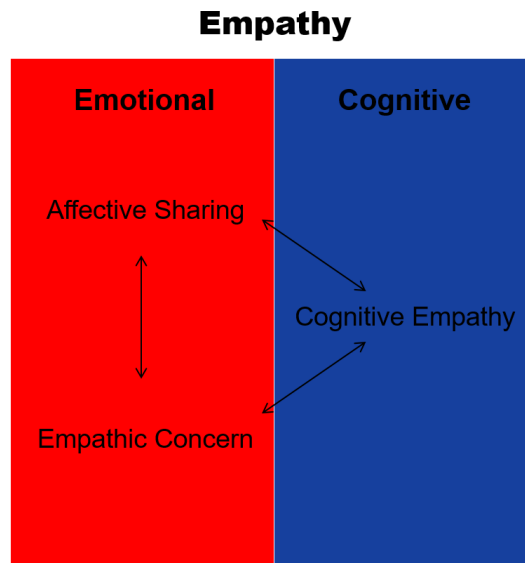


Figure 1.1 The conceptualization of empathy presently adopted

Empathy is believed to be a multidimensional construct subsuming partially dissociable but interacting components, including cognitive empathy, as well as affective sharing and empathic concern aspects of emotional empathy. There is evidence to suggest that cognitive and emotional empathy can bidirectionally modulate each other in an inhibitory or excitatory fashion.

1.2 Empathy Dysfunction

Investigations in clinical populations featuring empathy dysfunction can uniquely elucidate fundamental aspects of empathic responding (Blair, 2005; Marsh, 2013). More specifically, determining the aspects of empathy that are affected in particular disorders provides critical insight into the nature of empathy and associated behavioural disturbances. It also informs types of treatment or compensatory options that might be most beneficial for different patient populations. Empathy impairments are featured in many debilitating neurological, developmental, and psychiatric disorders, including frontotemporal dementia (Dermody et al.,

2016; Rankin et al., 2006), autism spectrum disorder (Baron-Cohen, Leslie, & Frith, 1985; Mathersul, McDonald, & Rushby, 2013b), schizophrenia (Green, Horan, & Lee, 2015), borderline personality disorder (Dziobek et al., 2011; Harari, Shamay-Tsoory, Ravid, & Levkovitz, 2010), and psychopathy (Blair, 2005). Of particular interest, loss of empathy is an early and salient discriminating feature of behavioural variant frontotemporal dementia (Rascovsky et al., 2011), including deficits in both cognitive and emotional empathy. Autism spectrum disorder and psychopathy are also especially informative as they have provided evidence for a double dissociation between cognitive and emotional empathy dysfunction, and are typically associated with more selective impairments in cognitive, and emotional, empathy, respectively. Further, subclinical autistic and psychopathic traits vary independently in the healthy population as well (J. Rogers, Viding, Blair, Frith, & Happe, 2006), and have been respectively inversely associated with cognitive, and emotional empathy, performance.

1.2.1 Empathy in behavioural variant frontotemporal dementia

Behavioural variant frontotemporal dementia (bvFTD) is a progressive neurodegenerative disorder caused by neuronal loss and aberrant protein accumulations in the prefrontal and anterior temporal cortex (Neary, Snowden, & Mann, 2005; Snowden, Neary, & Mann, 2002). Critically, this patient population is of particular interest because a loss of empathy is one of the core diagnostic features of bvFTD, and it is characterized by profound impairments in social and emotional behaviour (Rascovsky et al., 2011). These symptoms manifest early on in the disorder and are both highly debilitating to affected patients and distressing to caregivers (Boutoleau-Bretonniere et al., 2008; Diehl-Schmid et al., 2013; Levenson & Miller, 2007; Uflacker et al., 2016). For example, individuals with bvFTD often present with callousness, apathy, disinhibited behavior and speech, aggression, decline in manners and personal hygiene, impulsivity and reckless decision-making, and lack of insight (Finger, 2011, 2016). Further, brain areas thought to be critically involved in cognitive and emotional empathy are among the first to physically degenerate in these patients. More specifically, atrophy of the mPFC, as well as the anterior insula and anterior cingulate cortex is apparent even in very mild cases of bvFTD (Seeley et al., 2008), which are key areas consistently implicated in cognitive and emotional empathy, respectively (Bzdok et al., 2012; Fan et al., 2011; Shamay-Tsoory, 2011; Walter, 2012). Thus,

bvFTD presents a unique opportunity to answer fundamental questions about the nature of empathy and its constituents, at both a neural and behavioural level, due to the early and progressive deterioration of empathic abilities and their neural substrates (Levenson & Miller, 2007). Indeed, it has been recognized as a powerful model for the investigation of relationships between behaviour and neural activity (Wittenberg et al., 2008). These patients also represent a favourable group for the study of empathic dysfunction because their social deficits often precede decline in memory and visuospatial abilities (Finger, 2016), generally limiting the influence of such confounding factors at earlier disease stages. Further, though there is evidence for deficits in both cognitive and emotional empathy in patients with bvFTD, gaps in knowledge remain with regard to these impairments. Critically, highlighting potential treatment targets and a means to assess the impact of novel therapies on social and emotional impairment in bvFTD is of great importance being that there are currently no approved treatment options for these extremely debilitating socioemotional symptoms (Finger, 2011).

1.2.1.1 Cognitive empathy in behavioural variant frontotemporal dementia

Cognitive empathy and theory of mind impairments have been demonstrated using various measures in bvFTD. Specifically, caregiver questionnaires indicate lower perspective-taking scores, an index of cognitive empathy (Davis, 1980), for patients with bvFTD in comparison to healthy controls (Eslinger, Moore, Anderson, & Grossman, 2011; Rankin et al., 2006; Rankin et al., 2005) and patients with Alzheimer's disease (Fernandez-Duque, Hodges, Baird, & Black, 2010; Hsieh, Irish, Daveson, Hodges, & Piguet, 2013). Patients with bvFTD have also shown a deficit in mental state inference compared to healthy controls on performance-based cognitive empathy tasks, including false belief tasks (Gregory et al., 2002; Lough, Gregory, & Hodges, 2001), faux pas detection (Gregory et al., 2002; Torralva et al., 2007), theory of mind stories, cartoons, and videos (Eslinger et al., 2007; Shany-Ur et al., 2012; Torralva et al., 2007), and the Reading the Mind in the Eyes test (Couto et al., 2013; Gregory et al., 2002; Torralva et al., 2007). Though a cognitive empathy deficit is well-established in bvFTD, whether this impairment exists for both negative and positive mental states has yet to be investigated in this patient population.

1.2.1.2 Emotional empathy in behavioural variant frontotemporal dementia

There is also evidence for an emotional empathy deficit in bvFTD from several sources. In the past, the lack of behavioural indices of emotional empathy available made this dimension difficult to evaluate objectively, such that there were few performance-based assessments of emotional empathy in patients with bvFTD. An emotional empathy impairment in this patient group was instantiated based on lower empathic concern scores on caregiver questionnaires for patients with bvFTD as compared to healthy controls (Eslinger et al., 2011; Lough et al., 2006; Rankin et al., 2006) and patients with Alzheimer's disease (Fernandez-Duque et al., 2010; Hsieh et al., 2013), as well as an abundance of case descriptions reporting emotional blunting and heightened coldheartedness (Lough et al., 2001; Snowden et al., 2001; Thibodeau & Miller, 2013). Patients with bvFTD have also demonstrated reduced emotional reactivity in the form of lower blood pressure in response to a disgust-eliciting video than healthy controls (Eckart, Sturm, Miller, & Levenson, 2012). However, psychophysiological measures can be difficult to interpret being that the emotional response reflected by changes in arousal is ambiguous. Similarly, whether patients with bvFTD demonstrate a deficit in both affective sharing and empathic concern is unclear. Further, items on questionnaire measures of emotional empathy include predominantly negative situations rather than evaluating emotional empathy for positive mental states. Thus, as with cognitive empathy, it is uncertain whether the emotional empathy deficit in bvFTD is apparent for both negative and positive states.

1.2.1.3 Summary

Deficits in both cognitive and emotional empathy have been demonstrated in bvFTD. However, whether cognitive and emotional empathy are impaired for both negative and positive mental states is of particular interest being that these patients have shown impaired recognition of negative, but not positive, facial expressions (Fernandez-Duque & Black, 2005; Kipps, Mioshi, & Hodges, 2009; Kumfor et al., 2011; Lavenex, Pasquier, Lebert, Petit, & Van der Linden, 1999; Lough et al., 2006). Determining if this is a generalized impairment could provide insight into the neural representation of empathy and whether this varies according to valence. This information would also be beneficial for identifying treatment targets in affected patients. With regard to emotional empathy in particular, past investigations have largely utilized

questionnaire measures rather than behavioural paradigms for its evaluation. Thus, less is known about deficits in online empathic responding in bvFTD. Further, studies in this patient population have not included measures of both affective sharing and empathic concern, such that it remains unclear whether bvFTD is associated with impairments in both aspects of emotional empathy. Overall, there is a need to determine whether emotional valence may influence cognitive and emotional empathic responding in patients with bvFTD, and if they show impairments in both affective sharing and empathic concern. Critically, this may serve to increase insight into both fundamental aspects of empathy and the intricacies of empathy deficits in bvFTD.

1.2.2 Empathy in autism spectrum disorder versus psychopathy

Autism spectrum disorder (ASD) and psychopathy also present two disorders characterized by empathy deficits of particular interest. Specifically, these patient populations have been purported to provide evidence for a double dissociation between cognitive and emotional empathy dysfunction (Blair, 2008). Accordingly, they have the potential to provide critical insight into the fundamental nature of cognitive and emotional empathy, and their dissociability (Blair, 2005). Further, traits associated with these disorders have also been linked to variability in cognitive and emotional empathic responding in the healthy population.

1.2.2.1 Empathy in autism spectrum disorder

ASD is a developmental disorder characterized by social impairment and communication deficits, and a theory of mind or cognitive empathy deficit is one of its defining features (Baron-Cohen, 2000; Hill & Frith, 2003). Accordingly, individuals with ASD have shown cognitive empathy impairments across multiple paradigms, including false belief tasks (Baron-Cohen et al., 1985; Happe, 1995), faux pas detection (Baez et al., 2012; Stone et al., 1998), the Reading the Mind in the Eyes test (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Kirchner, Hatri, Heekeren, & Dziobek, 2011), and paradigms involving the inference of mental states or intentions from stories or vignettes (Happe, 1994; K. Rogers, Dziobek, Hassenstab, Wolf, & Convit, 2007) and animations (Abell, Happe, & Frith, 2000; White, Coniston, Rogers, & Frith, 2011). Further, individuals with ASD have shown

a deficit in cognitive empathy but intact emotional empathy, including ratings of subjective arousal and empathic concern, on the Multifaceted Empathy Test (Dziobek et al., 2008), as well as the Interpersonal Reactivity Index (Davis, 1980), a canonical empathy questionnaire measure with perspective taking (cognitive empathy) and empathic concern (emotional empathy) subscales (Baez et al., 2012; K. Rogers et al., 2007; Rueda, Fernandez-Berrocal, & Baron-Cohen, 2015). Adolescents with ASD have also been found to provide similar ratings of affective sharing (valence and arousal) and exhibit similar physiological arousal in response to emotional images compared to healthy controls (Louwerse et al., 2014; but see also Mathersul, McDonald, & Rushby, 2013a, 2013b; Shamay-Tsoory, Tomer, Yaniv, & Aharon-Peretz, 2002).

1.2.2.2 Empathy in psychopathy

Psychopathy is a developmental disorder characterized by callousness and emotional dysfunction paired with antisocial behaviour (Cleckley, 1967; Hare, 1991). Indeed, callous-unemotional traits are one of the primary features of psychopathy, including a lack of empathy, loyalty, and guilt (Frick, 1995; Hare, 1991). Impairments in emotional empathy in adults with psychopathy and youths with psychopathic tendencies have been inferred from reduced physiological emotional reactivity to distress cues (Anastassiou-Hadjicharalambous & Warden, 2008; Blair, 1999; Blair et al., 1997; de Wied, van Boxtel, Matthys, & Meeus, 2012), atypical neural activation in emotion-related brain areas in response to emotional stimuli (Decety, Skelly, Yoder, & Kiehl, 2014; Marsh et al., 2008), and emotion recognition deficits (Blair, Colledge, Murray, & Mitchell, 2001; Fairchild, Van Goozen, Calder, Stollery, & Goodyer, 2009; Hastings, Tangney, & Stuewig, 2008). However, what is responsible for driving these effects is ambiguous, and as such, whether they reflect a lack of affective sharing and/or empathic concern is unclear. In contrast, individuals with psychopathy have demonstrated intact theory of mind or cognitive empathy fairly consistently, on tasks including mental state inference from short stories (Blair et al., 1996), faux pas detection, false belief tasks, and questionnaire measures (Dolan & Fullam, 2004), and the Reading the Mind in the Eyes test (Richell et al., 2003).

1.2.2.3 Summary

Thus, psychopathy is thought to be particularly related to emotional empathy impairments and ASD is often specifically linked with cognitive empathy deficits (Blair, 2005; but see also Baron-Cohen, 2009; Grove, Baillie, Allison, Baron-Cohen, & Hoekstra, 2014; Mazza et al., 2014). Indeed, this double dissociation has been demonstrated using behavioural tasks tapping cognitive and emotional empathy in clinical samples of youths with ASD versus those with psychopathic tendencies (Jones et al., 2010; Schwenck et al., 2012). However, regarding emotional empathy, whether psychopathic traits are differentially linked to affective sharing versus empathic concern remains unclear. This is of particular importance being that multiple phenomena are referred to using the term empathy, and these may have different implications for social behaviour. It is also of interest to determine whether these phenomena may vary independently in some disorders. Interestingly, autistic and psychopathic traits also vary in the healthy population and have been associated with reduced cognitive and emotional empathy, respectively, which raises the possibility of gaining valuable insight into differences in components of empathic responding in community samples.

1.3 Empathic Variability and Subclinical Traits

1.3.1 Empathy, and autistic and psychopathic traits in the healthy population

Much work has been done to investigate empathic abilities in patient populations. However, less is known about the relationship between particular traits linked with empathy deficits in clinical samples and empathic responding in healthy individuals. Interestingly, evidence suggests that both autistic (Constantino & Todd, 2003; Posserud, Lundervold, & Gillberg, 2006) and psychopathic (Edens, Marcus, Lilienfeld, & Poythress, 2006; Hare & Neumann, 2008) traits vary continuously in the general population, and can vary independently of one another (J. Rogers et al., 2006). Nonetheless, evidence is limited as to how individual differences in these traits map onto components of empathic responding. In non-clinical samples, individuals with high affective-interpersonal psychopathic trait levels have demonstrated lower emotional empathy scores on questionnaire measures (Mahmut, Homewood, & Stevenson, 2008), dampened empathic responding to emotional faces and stories (Seara-Cardoso, Dolberg,

Neumann, Roiser, & Viding, 2013; Seara-Cardoso, Neumann, Roiser, McCrory, & Viding, 2012), and functional abnormalities in affect-related neural regions in response to emotional stimuli (Han, Alders, Greening, Neufeld, & Mitchell, 2011; Harenski, Kim, & Hamann, 2009). Alternatively, autistic traits have been inversely correlated with cognitive empathy performance in neurotypical adults (Baron-Cohen et al., 2001; Miu, Pana, & Avram, 2012; Voracek & Dressler, 2006). Bridging this evidence, high autistic traits have been associated with diminished theory of mind performance, whereas high psychopathic traits have been linked to dampened affective resonance in the same community sample (Lockwood et al., 2013). However, a measure of empathic concern was not included in this investigation. As mentioned, little is known about the dissociability of affective sharing and empathic concern, and most investigations do not distinguish between these two components, often using emotional empathy to refer to either. Thus, the relationship between autistic versus psychopathic traits with different components of empathy has rarely been examined in the same sample of healthy individuals. Accordingly, it remains unknown whether coldhearted psychopathic and autistic traits in a community sample are differentially associated with cognitive empathy, empathic concern, and affective sharing performance.

1.3.2 Empathy and anxious traits in the healthy population

In addition to psychopathic and autistic traits, trait anxiety varies continuously in the general population (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). Trait anxiety may have important implications for empathy, as arousal is widely considered to be a component of empathic responding (Decety, Norman, Berntson, & Cacioppo, 2012; Decety, Smith, Norman, & Halpern, 2014). Accordingly, high questionnaire scores of emotional empathy in healthy individuals have been associated with increased autonomic arousal in response to emotional stimuli (Balconi & Bortolotti, 2012b; Bogdanov et al., 2013; de Sousa et al., 2010; Mehrabian, Young, & Sato, 1988). Indeed, as mentioned, autonomic arousal is sometimes used as an emotional empathy index (Blair et al., 1997; de Wied et al., 2009; Eisenberg & Fabes, 1990); though this can be problematic because it is unclear what this physiological arousal reflects. Lastly, amygdala activation has been differentially linked with levels of trait anxiety (Stein, Simmons, Feinstein, & Paulus, 2007) and emotional empathy (Seara-Cardoso, Sebastian, Viding,

& Roiser, 2015), indicating that there may be overlap in their neurocognitive substrates. However, very little work exists concerning individual differences in trait anxiety and the elicitation of empathy. Thus, though trait anxiety may be theoretically important for empathic responding, studies rarely include measures of both anxiety and empathy, and their relationship has been the focus of few investigations.

1.3.3 Summary

Evidence from patients with ASD and psychopathy suggests that these disorders are differentially linked with deficits in cognitive and emotional empathy, respectively. Limited evidence has also suggested that cognitive and emotional empathy may vary as a function of autistic and psychopathic traits in the healthy population. However, the relationship between psychopathic versus autistic traits with dissociable empathy indices has rarely been examined in healthy individuals. Crucially, no study to date has assessed cognitive empathy, affective sharing, and empathic concern performance in relation to individual differences in autistic, psychopathic, and anxious traits in the same group of healthy individuals. Elucidating these associations at a more refined level is critical given that the term empathy is used to refer to multiple phenomena that relate differentially to social behavioural outcomes. It will also provide insight into whether subclinical levels of these traits influence different components of empathic responding. In addition, this would allow for the examination of whether psychopathic traits are associated with deficits in both affective sharing and empathic concern aspects of emotional empathy. For example, a selective deficit in affective sharing but not empathic concern might result in an individual feeling afraid in response to another individual's fear, but lacking concern for the victim or the desire to reduce their distress. Lastly, the inclusion of trait anxiety measures would uniquely elucidate the relationship between emotional empathy and trait anxiety. Trait anxiety is implicated in arousal and may be associated with empathy on both a neurocognitive and conceptual level, such that this may have significant implications for models of empathy and their relationship to neurocognitive systems involved in trait anxiety. This could also have important implications for the use of arousal indices and their interpretation in empathy investigations.

1.4 Neurocognitive Mechanisms of Empathy

Though the brain areas associated with cognitive and emotional empathy have been fairly well-established, the neural mechanisms underlying empathic responding remain unclear. Given evidence for the dissociability of cognitive and emotional empathy, elucidating their underlying mechanisms is critical for developing targeted treatment or compensatory options for patients featuring deficits in either of these facets of empathy. Many believe that empathy involves both bottom-up and top-down processing (Decety & Meyer, 2008; Preston & de Waal, 2002; Shamay-Tsoory, 2011; Singer & Lamm, 2009; Tousignant, Eugene, & Jackson, 2016). More specifically, it has been proposed that bottom-up processing occurs automatically in response to perceptual or sensory information, involving an action-perception matching mechanism. Alternatively, top-down processing is thought to underlie the projection of oneself into another's situation. It involves the incorporation of an individual's intentions, motivation, and self-regulation, and is believed to influence the degree of empathic responding and resultant outcomes, such as prosocial and moral behaviour (Decety & Cowell, 2014b; Decety & Meyer, 2008; Decety & Moriguchi, 2007). Emotional empathy, and affective sharing in particular, are commonly thought to be largely dependent on bottom-up processing, whereas cognitive empathy is believed to rely more on top-down processing (Decety & Jackson, 2004; Decety & Meyer, 2008). However, these processes are not purported to map exclusively onto emotional and cognitive facets of empathy and may not have entirely disparate neural circuitry, such that they may be involved in the experience of both (Decety, 2011; Shamay-Tsoory, 2011). More specifically, it has been suggested that simulation mechanisms involving action-perception matching, a form of bottom-up processing, may contribute to both cognitive and emotional empathy.

1.4.1 Empathy and simulation

Despite evidence for the dissociability of cognitive and emotional empathy, it is still debated whether they rely on some of the same neurocognitive mechanisms. Specifically, and consistent with bottom-up processing, some advocate that empathy is the result of shared representations, and the activation of similar neural substrates during the observation of behaviour as during the execution of such behaviour (Bastiaansen, Thioux, & Keysers, 2009; Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Gallese, 2001; Gallese, Keysers, &

Rizzolatti, 2004; Iacoboni, 2009; Pineda, Moore, Elfenbein, & Cox, 2009; Preston & de Waal, 2002). The discovery of mirror neurons in the ventral premotor cortex (PMC) into inferior frontal gyrus (IFG), and inferior parietal lobule (IPL) of macaque monkeys, which fire during both action observation and action execution, provided a potential physiological substrate for such an action-perception matching mechanism (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Fogassi et al., 2005; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). There is evidence to suggest that a similar system exists in humans, which responds to both the perception and execution of actions, including the ventral PMC into IFG and the IPL (Caspers, Zilles, Laird, & Eickhoff, 2010; Molenberghs, Cunnington, & Mattingley, 2012). The posterior superior temporal sulcus (STS), though not believed to contain these observation-execution matching neurons and instead responding selectively to action observation, is thought to provide the visual input to these two critical simulation regions (Iacoboni et al., 2001; Keysers & Perrett, 2004). Presently, this circuitry, including the ventral PMC into IFG, the IPL, and the posterior STS, is referred to as the 'simulation network' (Figure 1.2). Of particular note, increased activation in critical frontal and parietal areas of the simulation network has been demonstrated during the observation and imitation of emotional expressions (Carr et al., 2003; Leslie, Johnson-Frey, & Grafton, 2004; Montgomery & Haxby, 2008), suggesting that these regions may generate a motor representation of the emotional or mental states of others. Although there is some evidence to suggest that cognitive and emotional empathy may rely on simulation mechanisms, this remains unsettled. Thus, it is of particular interest to determine the relative contribution, if any, of simulation mechanisms to these dissociable facets of empathy.

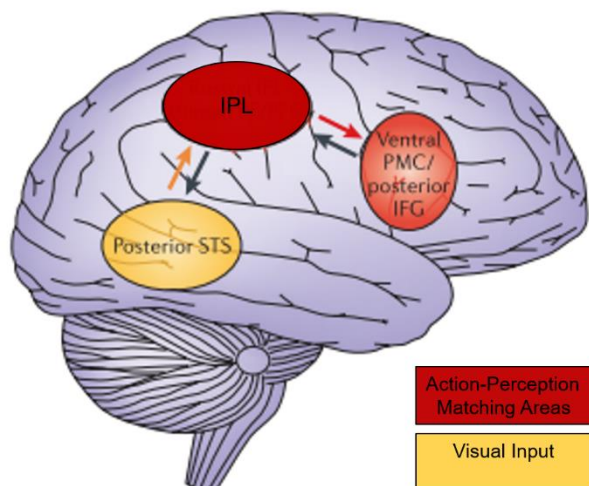


Figure 1.2 The simulation network

A depiction of the regions comprising the simulation network, including action-perception matching areas considered critical for simulation, and the visual input to these areas. Figure adapted by permission from Macmillan Publishers Ltd: Nature Reviews Neuroscience (Iacoboni & Dapretto, 2006). PMC, premotor cortex; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; STS, superior temporal sulcus.

1.4.1.1 Cognitive empathy and simulation

Some have proposed that the simulation network may underlie cognitive empathy, with simulation allowing one to adopt the perspective of another and thereby understand their mental state (Agnew, Bhakoo, & Puri, 2007; Gallese, 2001; Gallese & Goldman, 1998; Pineda et al., 2009; Rizzolatti & Sinigaglia, 2010). More specifically, it has been suggested that the simulation network may influence cognitive empathy via the posterior STS/TPJ, rapidly providing goal-related information from perceived actions (Tramacere & Ferrari, 2016; Van Overwalle, 2009). The simulation network has been implicated in aspects of cognitive empathy including intention understanding and mental state attribution. Early evidence suggested that the simulation network, and the IFG in particular, was sensitive to the intended goal of actions rather than merely actions themselves (Iacoboni et al., 2005; Kaplan & Iacoboni, 2006). Activity in putative simulation regions has also been observed during mental state inference tasks (Lawrence et al., 2006; Pineda

& Hecht, 2009). Indeed, one investigation found that mental state attribution accuracy modulated activity in simulation regions (Zaki, Weber, Bolger, & Ochsner, 2009). However, another failed to find modulation of activity in these regions based on mental state content in participants' descriptions of others' actions (Spunt, Satpute, & Lieberman, 2011). Of particular interest, a conjunction analysis between a cognitive empathy animation task and an action observation task used to localize simulation areas has revealed overlap in the posterior STS, but not the critical simulation regions of the IFG or IPL (Ohnishi et al., 2004). Accordingly, many fMRI investigations of cognitive empathy fail to find significant activation in putative critical simulation areas (Van Overwalle & Baetens, 2009). Thus, findings are mixed regarding the role of the simulation network in cognitive empathy.

1.4.1.2 Emotional empathy and simulation

It has also been proposed that the simulation network may influence parts of the limbic system and emotional experience via connections between the IFG and the insula, to mediate emotional empathy (Carr et al., 2003). Indeed, some accounts have adopted the view that simulation mechanisms are particularly involved in the experience of emotional empathy rather than cognitive empathy (Dvash & Shamay-Tsoory, 2014; Molnar-Szakacs, 2011; Shamay-Tsoory, 2011). Evidence in support of this comes largely from demonstrations of positive associations between questionnaire measures of emotional, but not cognitive, empathy, and IFG activity during the observation and imitation of emotional expressions (Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008), right IFG and IPL gray matter volume (Cheng et al., 2009), and white matter integrity in a tract connecting inferior frontal and temporoparietal regions (Parkinson & Wheatley, 2014). Of particular relevance, an fMRI investigation of cognitive and emotional empathy interpreted greater engagement of the PMC during emotional empathy than cognitive empathy as evidence for greater engagement of the simulation network (Nummenmaa, Hirvonen, Parkkola, & Hietanen, 2008). However, to date there is a void of evidence directly relating online emotional empathy to activity in localized simulation regions (Baird, Scheffer, & Wilson, 2011; Decety, 2010; Lamm & Majdandzic, 2015).

1.4.1.3 Summary

Overall, there is some support for a greater role of the simulation network in emotional versus cognitive empathy, but the degree to which simulation is involved in these different facets remains unclear. This is due to the fact that prior studies have largely provided evidence in the form of correlations between questionnaire measures of empathy and activity in identified simulation regions, which do not provide insight into online empathic responding and its neural correlates. Evidence also comes from activation during empathy tasks in vast regions broadly accepted as being part of the simulation network, rather than functionally defined regions of interest based on simulation involvement. Critically, the involvement of the simulation network in cognitive versus emotional empathy has never been statistically compared. Further, no studies to date have utilized functional localizers to determine the correspondence between brain areas identified as having simulation properties, and those recruited during cognitive and emotional empathy within the same participant population. Such steps are necessary in order to confirm that regions being interrogated with regard to their involvement in simulation are indeed those engaged during a simulation task, and to resolve whether these areas are preferentially involved in emotional versus cognitive empathy.

Determining the involvement of the simulation network in cognitive versus emotional empathy could provide unique insight into the mechanisms underlying different facets of empathy, and the contributions of bottom-up processing to these components. This would serve to elucidate the nature of empathy and daily interpersonal interactions. Further, it could be particularly crucial for identifying potential compensatory options or targeted treatments for individuals with cognitive and emotional empathy impairments.

1.5 Thesis Objectives and Hypotheses

The **overall objective** of this thesis is to elucidate the nature of different components of empathy and how they vary as a function of clinical diagnoses and individual differences in subclinical traits, as well as their underlying functional neural mechanisms. Three independent studies were conducted to address this overall goal using a multifaceted approach to investigate the behavioural and functional neural correlates of different facets of empathy in the healthy

population and patients featuring empathy deficits. The **central hypothesis** is that cognitive empathy, and aspects of emotional empathy including affective sharing and empathic concern, represent distinguishable components of empathic responding that are differentially associated with particular disorders, traits, and neurocognitive mechanisms. More specifically, it is predicted that aspects of empathy can be differentially affected in clinical populations characterized by empathy dysfunction, and differentially associated with traits in the healthy population. Lastly, it is expected that cognitive and emotional facets of empathy will involve action-perception matching, simulation mechanisms to different degrees.

1.5.1 Study I - Parsing cognitive and emotional empathy deficits for negative and positive stimuli in frontotemporal dementia

Examining empathy impairments in clinical populations can provide insight into the fundamental nature of empathy, and the dissociability of its components. Accordingly, bvFTD is a debilitating neurodegenerative disorder characterized by empathy impairments. Both cognitive and emotional empathy deficits have been associated with bvFTD. However, little work has focused on the performance of patients with bvFTD on behavioural measures of emotional empathy, and whether empathic responses differ for negative versus positive stimuli. The objective of this study was to examine empathy for negative and positive mental states in bvFTD. We utilized the Multifaceted Empathy Test, a performance-based task that taps cognitive empathy, affective sharing, and empathic concern components of empathy, and allows for the discrimination of responses to negative versus positive realistic images. This represents the first time this task has been utilized in patients with FTD, and allowed for emotional empathy to be assessed based on behavioural responses to naturalistic images. We hypothesized that patients with bvFTD would demonstrate impaired cognitive empathy based on consistent evidence from the literature to date, and an emotional empathy deficit based largely on caregiver and clinical reports of patient behaviour. We also predicted that cognitive and emotional empathy would be more impaired for negative stimuli compared to positive stimuli, based on some evidence of a selective deficit in recognizing negative emotional expressions in bvFTD (Fernandez-Duque & Black, 2005; Kipps et al., 2009). Beyond providing unique insight into the empathy impairment associated with bvFTD, this could also elucidate whether valence is influential in the

representation of particular aspects of empathy, as well as the potential dissociability of these components.

1.5.2 Study II - Distinguishing the relationship between different aspects of empathic responding as a function of psychopathic, autistic, and anxious traits

Although cognitive and emotional empathy impairments have been associated with specific developmental and neurological disorders, such as ASD and psychopathy, respectively, little is known about how performance-based measures of cognitive empathy, affective sharing, and empathic concern relate to individual differences in autistic, psychopathic, and anxious traits in the healthy population. In particular, investigations of empathic responding rarely distinguish between different aspects of emotional empathy, or consider the potential impact of anxiety. Based on the findings of differential deficits in components of empathy in patients with bvFTD from Study I, we were particularly interested in the potential dissociability of cognitive empathy, affective sharing, and empathic concern in a community sample. Accordingly, there were two main objectives of this investigation. First, we sought to determine whether autistic and coldhearted psychopathic traits in a community sample were differentially related to cognitive empathy, affective sharing, and empathic concern performance. Our second goal was to elucidate the relationship between trait anxiety and empathy. Healthy adults completed the Multifaceted Empathy Test, a performance-based task tapping cognitive empathy and multiple aspects of emotional empathy, as in Study I, as well as trait questionnaire measures. It was hypothesized that coldhearted psychopathic traits, which reflect the core emotional features of psychopathy, including a lack of empathy (Lilienfeld & Widows, 2005), would be negatively correlated with emotional empathy ratings, including both affective sharing and empathic concern, but not cognitive empathy performance. Alternatively, we expected autistic trait levels to be inversely associated with cognitive empathy performance, but not emotional empathy ratings. Lastly, it was predicted that trait anxiety would be positively related to emotional empathy, but that this would be driven by an association with measures of affective sharing, and arousal ratings in particular. The identification of differential relationships between aspects of empathy and subclinical traits provides insight into their dissociability, as well as their potential behavioural outcomes and neural substrates.

1.5.3 Study III - The neurocognitive correlates of distinct facets of empathy: Greater involvement of simulation mechanisms in emotional relative to cognitive empathy

Findings from Studies I and II provided compelling evidence for the distinguishability of cognitive empathy, affective sharing, and empathic concern components of empathy. This contributes to a large body of evidence suggesting that cognitive and emotional empathy facets are dissociable. Despite this, whether these processes rely on different underlying mechanisms is still debated. Specifically, it has been suggested that action-perception neural matching, or simulation mechanisms, may facilitate empathy by supporting the simulation of perceived experience in others. Though there is some support for a role of the simulation network in cognitive empathy, evidence suggests that it is preferentially involved in emotional empathy. However, this remains unclear, and no studies to date have statistically compared the involvement of the simulation network in these two facets of empathy. Thus, the objective of this study was to delineate the involvement of the simulation network in cognitive and emotional empathy. Healthy adults underwent fMRI while completing tasks targeting cognitive empathy, emotional empathy, and the simulation network. Critically, this marks the first use of functional localizers to determine the common recruitment among brain areas identified as having simulation properties, and those engaged during cognitive and emotional empathy within the same sample. Our central hypothesis was that critical regions for action-perception matching within the simulation network would be more involved in the facilitation of emotional than cognitive empathy. Specifically, localized regions of the simulation network were predicted to show some overlap with areas engaged by both the cognitive and emotional empathy tasks. However, critical simulation areas, including the ventral PMC/IFG and IPL, were expected to be recruited to a greater degree during emotional as compared to cognitive empathy. Lastly, performance on the emotional empathy task was expected to be more strongly associated with activity in the simulation network than performance on the cognitive empathy task.

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Chapter 2

2 Parsing Cognitive and Emotional Empathy Deficits for Negative and Positive Stimuli in Frontotemporal Dementia¹

Abstract

Objectives: Behavioural variant frontotemporal dementia (bvFTD) is a debilitating neurodegenerative disorder characterized by frontal and temporal lobe atrophy primarily affecting social cognition and emotion, including loss of empathy. Many consider empathy to be a multidimensional construct, including cognitive empathy (the ability to adopt and understand another's perspective) and emotional empathy (the capacity to share another's emotional experience). Cognitive and emotional empathy deficits have been associated with bvFTD; however, little is known regarding the performance of patients with bvFTD on behavioural measures of emotional empathy, and whether empathic responses differ for negative versus positive stimuli.

Methods: 24 patients with bvFTD and 24 healthy controls completed the Multifaceted Empathy Test (MET; Dziobek et al., 2008), a performance-based task that taps both cognitive and emotional facets of empathy, and allows for the discrimination of responses to negative versus positive realistic images. MET scores were also compared with caregiver ratings of patient behaviour on the Interpersonal Reactivity Index, which assesses patients' everyday demonstrations of perspective taking and empathic concern.

Results: Patients with bvFTD were less accurate than controls at inferring mental states for negative and positive stimuli. They also demonstrated lower levels of shared emotional experience, more positive emotional reactions, and diminished arousal to negative social stimuli relative to controls. Patients showed reduced emotional reactions to negative non-social stimuli as well. Lastly, the MET and IRI measures of emotional empathy were found to be significantly correlated within the bvFTD group.

¹ Chapter 2 is modified from its published format as: Oliver, L. D., Mitchell, D. G. V., Dziobek, I., MacKinley, J., Coleman, K., Rankin, K. P., & Finger, E. C. (2015). Parsing cognitive and emotional empathy deficits for negative and positive stimuli in frontotemporal dementia. *Neuropsychologia*, 67, 14-26.

Conclusions: The results suggest that patients with bvFTD show a global deficit in cognitive empathy, and deficient emotional empathy for negative, but not positive, experiences. Further, a generalized emotional processing impairment for negative stimuli was observed, which could contribute to the emotional empathy deficit. This work highlights potential treatment targets and a means to assess the impact of novel therapies on socioemotional impairment in bvFTD.

2.1 Introduction

Frontotemporal dementia (FTD) is a debilitating neurodegenerative disorder characterized by progressive deterioration of the frontal and temporal lobes, for which there is presently no cure. There are several variants of FTD, including behavioural variant (bv) FTD, semantic dementia, and progressive non-fluent aphasia (PNFA). Patients with bvFTD present with early, strikingly dysfunctional social and emotional behaviour, including disinhibition and impulsivity, lack of insight, and emotional blunting, callousness, and a loss of empathy (Gustafson, 1987; Neary, Snowden, & Mann, 2005). Notably, patients with semantic dementia with right temporal lobe atrophy also tend to demonstrate similar behavioural symptoms early in the course of illness (Bozeat, Gregory, Ralph, & Hodges, 2000; Seeley et al., 2005; Snowden et al., 2001), and all three subtypes can include these behavioural abnormalities (Neary et al., 1998; Rosen et al., 2006).

One of the core diagnostic features of bvFTD is a loss of empathy, exhibited by decreased social interest, diminished responsiveness to the feelings of others, and increased coldheartedness (Perry & Miller, 2001; Rascovsky et al., 2011). Empathy has been defined as “an affective response more appropriate to another’s situation than one’s own” (Hoffman, 1987, p. 48), or an affective response similar to another individual’s feelings based on the comprehension of their emotional state (Eisenberg, Shea, Carlo, & Knight, 1991). It is considered to be a multidimensional construct by many, including both cognitive and emotional facets (Davis, 1980; Eslinger, 1998). Some have argued for the existence of an additional facet termed motor empathy, referring to inherent mirroring of the movements and facial expressions of others (e.g., Blair, 2005), though cognitive and emotional aspects are more traditionally considered. Cognitive empathy is sometimes used interchangeably with theory of mind (Blair, 2005; Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004), and refers to the ability to adopt another individual’s perspective, and thereby infer their mental or emotional state. Emotional empathy refers to the capacity to share and react affectively to the emotional experience of another individual. The dissociation of these facets is supported by behavioural, functional imaging, and lesion studies. For example, an emotional empathy deficit but intact cognitive empathy has been demonstrated in individuals with high psychopathic traits, whereas individuals with high autistic traits have been found to show the reverse pattern (Lockwood, Bird, Bridge, &

Viding, 2013). Further, tasks tapping cognitive empathy versus emotional empathy have been found to result in different patterns of activation (Fan, Duncan, de Greck, & Northoff, 2011; Shamay-Tsoory, 2011). Accordingly, patients with lesions to the ventromedial prefrontal cortex have shown impaired cognitive empathy and intact emotional empathy, whereas patients with inferior frontal gyrus lesions have demonstrated an emotional empathy deficit but intact cognitive empathy (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009).

Considerable evidence exists for impaired cognitive empathy and theory of mind in bvFTD, while a smaller number of studies have shown deficits on emotional empathy measures as well. Cognitive empathy impairments in bvFTD have been identified using both performance-based measures and caregiver ratings. For example, relative to controls, patients with bvFTD have demonstrated deficiencies in inferring the mental state, beliefs, and/or intentions of characters in false belief tasks (Lough, Gregory, & Hodges, 2001), humorous cartoons (Lough et al., 2006; Snowden et al., 2003), and vignettes of social scenarios (Eslinger et al., 2007; Shany-Ur et al., 2012). During one such task, termed the Faux pas test (Stone, Baron-Cohen, & Knight, 1998), participants are read short stories. Patients with bvFTD have shown a deficit in understanding whether a social faux pas has occurred based on representing the mental states of characters in the stories (Gregory et al., 2002; Torralva et al., 2007). Patients with bvFTD have also exhibited impaired theory of mind via poorer performance on the Reading the Mind in the Eyes test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) relative to controls (Couto et al., 2013; Gregory et al., 2002; Torralva et al., 2007), in which participants are shown the eye region of a face and asked to best identify what the individual is feeling from two or four choices, and the Judgment of Preference Task, in which participants are presented with a face whose eyes are directed at one of four objects and asked which object the face likes best (Snowden et al., 2003). Additionally, patients with bvFTD have been found to score lower on the Perspective Taking subscale of the Interpersonal Reactivity Index, according to caregiver ratings of patient behaviour, relative to controls (Eslinger, Moore, Anderson, & Grossman, 2011; Rankin et al., 2006; Rankin, Kramer, & Miller, 2005) and patients with Alzheimer's disease (Fernandez-Duque, Hodges, Baird, & Black, 2010; Hsieh, Irish, Daveson, Hodges, & Piguet, 2013). While these studies confirm that patients with bvFTD have a cognitive empathy deficit, little is known about whether this impairment is present for both negative and positive mental states. Patients with bvFTD are known to have significant deficits in the recognition of negative facial

expressions such as fear and sadness, whereas identification of positive expressions such as happiness is often relatively preserved (Fernandez-Duque & Black, 2005; Kipps, Mioshi, & Hodges, 2009; Kumfor et al., 2011; Lavenu, Pasquier, Lebert, Petit, & Van der Linden, 1999; Lough et al., 2006). As facial expression processing is likely one important component of the recognition of other's mental states, it is possible that patients with bvFTD may present with a more pronounced deficit in cognitive empathy for negative mental states. However, the distinction between cognitive empathy in response to negative versus positive stimuli has yet to be investigated in bvFTD.

Evidence of a deficit in emotional empathy, or the ability to share and react affectively to another individual's emotional experience, has also been reported in bvFTD using caregiver measures and clinical assessments. However, there have been few performance-based assessments of emotional empathy in this patient group. Caregivers completing the Interpersonal Reactivity Index (IRI; Davis, 1980), a multidimensional questionnaire assessing four components of empathy, report lower scores on the Empathic Concern subscale (i.e., feelings of concern, warmth, and compassion for less fortunate others) for patients with bvFTD in comparison to controls (Eslinger et al., 2011; Lough et al., 2006; Rankin et al., 2006) and patients with Alzheimer's disease (Fernandez-Duque et al., 2010; Hsieh et al., 2013). Reports of increased coldheartedness and emotional blunting also abound in detailed case descriptions (Lough et al., 2001; Snowden et al., 2001; Thibodeau & Miller, 2013). The paucity of objective measures of emotional empathy makes this a difficult dimension to objectively evaluate. Though emotion recognition likely captures aspects of emotional empathy and has been used as an index of emotional empathy in some populations (Blair, 2013), we are particularly interested in the affective response and/or shared emotional experience generated as a result of the emotional experience of another individual. Physiological measures, such as facial electromyography, skin conductance, heart rate, and blood pressure, are another avenue to assess emotional empathy or emotional reactivity. In patients with bvFTD, reduced blood pressure has been observed relative to controls in response to a disgust-eliciting video (Eckart, Sturm, Miller, & Levenson, 2012). However, such techniques can be challenging in patients with bvFTD, and may require additional means to determine the specific emotional response reflected by changes in arousal and related psychophysiological measures. Furthermore, items on the Empathic Concern subscale of the IRI include predominantly negative scenarios, and do not assess the potential for

empathy for positive mental states. Thus, similar to cognitive empathy, it is unclear whether emotional empathic deficits are specific to negative mental states of others, or may be found for both negative and positive states.

The present study was undertaken in order to examine empathy for negative and positive mental states in bvFTD using a performance-based measure, the Multifaceted Empathy Test (MET; Dziobek et al., 2008). The MET is a multidimensional empathy measure previously validated in healthy adults and patients with autism (Dziobek et al., 2008), which is designed to tap both cognitive and emotional facets of empathy in a dissociable way. Specifically, it includes questions that require mental state inference, and separate ratings of participants' emotional responses to realistic emotionally charged images. However, it should be noted that physiological responding is not measured during the task, and thus the degree to which participants' emotional empathy responses are independent from other cognitive response strategies cannot be completely delineated. The MET also allows for the discrimination of empathic responses to negative versus positive stimuli. Thus, the MET allows for the evaluation of both cognitive and emotional empathy, for negative and positive experiences, using a single task. This represents the first time this task has been utilized in patients with FTD, and will allow for emotional empathy to be assessed based on behavioural responses to naturalistic images. As well, the ability to distinguish between empathic responses to negative and positive stimuli is of particular interest based on some evidence of a selective deficit in recognizing negative emotional expressions in bvFTD with relatively intact positive emotion recognition (Fernandez-Duque & Black, 2005; Kipps, Mioshi, et al., 2009). In addition, there have been recent reports of less negative valence ratings being given to negative emotional pictures, with typical ratings of positive and neutral images, in patients with bvFTD (St. Jacques, Grady, Davidson, & Chow, 2014). We predicted that patients with bvFTD would show a deficit in cognitive empathy based on the consistent evidence from the existing literature, as well as an emotional empathy impairment based largely on clinical presentations and caregiver reports of patient behaviour. We also hypothesized that deficits in cognitive and emotional empathy would be more pronounced for negative stimuli compared to positive stimuli. In addition, caregivers were asked to complete the IRI in order to determine whether performance-based and caregiver-reported measures of empathy for negative experiences would be correlated in patients with bvFTD.

2.2 Methods

2.2.1 Participants

Forty-eight participants took part in this study, including 24 patients with bvFTD (12 male, 12 female) and 24 healthy volunteers (10 male, 14 female). All participants in the bvFTD group had abnormalities in social behaviour and emotional blunting as indexed on the Frontal Behavioural Inventory. All participants in the bvFTD group presented with behavioural symptoms meeting the revised international consensus diagnostic criteria for bvFTD (Rascovsky et al., 2011). Five patients with dual diagnoses of bvFTD and another FTD subtype were included [three patients with features of semantic dementia who had predominantly right temporal lobe atrophy, one patient with bvFTD and PNFA (Gorno-Tempini et al., 2011), and one patient with bvFTD, PNFA, and corticobasal syndrome (Armstrong et al., 2013)]. As a part of their initial clinical evaluation all patients completed cognitive testing assessing attention, memory, executive functioning, language, and visuospatial skills, and had magnetic resonance imaging, computed tomography, or single-photon emission computed tomography imaging consistent with the diagnoses. Diagnoses were made by a trained neurologist (ECF or AK). Patients were recruited through the Cognitive Neurology and Alzheimer Research Centre at Parkwood Hospital in London, Ontario, Canada. Age-matched control participants were recruited through advertisements to caregivers at local FTD family support groups and volunteer databases of the centre. All participants and caregivers provided written informed consent. This study was approved by the Health Sciences Research Ethics Board at the University of Western Ontario, London, Ontario, Canada.

2.2.2 Measures

2.2.2.1 Addenbrooke's Cognitive Examination - Revised (ACE-R; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006)

The ACE-R was administered to participants in order to assess non-social cognitive functioning, and whether this might differ between patients with bvFTD and the healthy control group. The ACE-R evaluates five cognitive domains, including attention/orientation, memory, verbal fluency, language, and visuospatial abilities. The Mini-Mental State Examination (MMSE), a screening tool for cognitive impairment in older adults, is also included in the examination. All participants had complete MMSE data. For one patient and two control participants the ACE-R was not completed alongside the initial MET testing, and we were unable to attain concurrent measures due to logistical reasons.

2.2.2.2 Multifaceted Empathy Test (MET; Dziobek et al., 2008; Figure 2.1)

The MET was administered to all participants in order to evaluate empathy multi-dimensionally. The MET is a performance-based measure which taps both cognitive and emotional facets of empathy in a dissociable way, and allows for the discrimination of empathic responses to negative versus positive stimuli. It consists of a series of images of realistic situations, about which participants are asked to answer a number of questions. Research staff administered the task using Microsoft PowerPoint and controlled slide presentation, recording the participant's responses as they voiced them aloud. Alternatively, two patients preferred to respond by pointing to the screen and another preferred to respond via button press. Each question was displayed on a separate slide that also displayed the relevant image. All ratings were provided using a 9-point Likert scale with pictograms from the Self-Assessment Manikin (Lang, Bradley, & Cuthbert, 1997). Completion of the MET required approximately 45 minutes. Stimuli include 23 pairs of naturalistic pictures (14 negative, 9 positive): a context-only image that is presented first, and a social image with a person or people embedded in this context expressing a relevant emotion that appears later. For each context-only picture, participants are asked 'How positive or negative does this picture make you feel?' (valence rating; 1 = most positive, 9 = most negative), and 'How calm or aroused does this picture make you feel?' (arousal rating; 1 = most calm, 9 = most aroused). For the social stimuli, participants are asked to

identify how the person or people in the picture are feeling (i.e., ‘How do you think this person is feeling?’) from four possible mental state descriptor choices as a measure of cognitive empathy accuracy. Feedback is then provided to ensure that improper mental state inference does not drive subsequent emotional responses to the stimulus. Participants subsequently provide a cognitive empathy intensity rating by indicating the degree to which they think the person is experiencing the given emotion (e.g., ‘How miserable do you think this person feels?’). The correct mental state descriptors, as well as the distractor options with the same valence, were chosen by consensus of a psychiatrist and three psychologists for each social image (Dziobek et al., 2008). Twenty-one unique mental state descriptors are included in the task. To capture the empathic concern component of emotional empathy, participants rate their emotional reactions to the stimuli, including how happy they are for the people (i.e., ‘How happy are you for this person?’ for positive stimuli), or their level of concern for them (i.e., ‘How concerned are you for this person?’ for negative stimuli). In addition, affective sharing is evaluated by asking participants to indicate the degree to which they share the emotional experience of the people in the photographs (intensity rating; e.g., ‘When looking at this picture, does it make YOU feel miserable at all? If so, how miserable do you feel?’), how positive or negative they feel in reaction to the stimuli (valence rating), and how calm or aroused they feel in response to the stimuli (arousal rating). A summary of measures included in the MET with example questions and responses are presented in Table 2.1. As mentioned, objective measures of physiological responding to the emotional stimuli were not included. Measures of affective sharing, which could be considered more implicit or indirect indices of emotional empathy, as well as empathic concern, a more explicit or direct measure of emotional empathy, were included in attempts to decrease socially desirable responding and the degree of introspection required throughout the task (Dziobek et al., 2008).

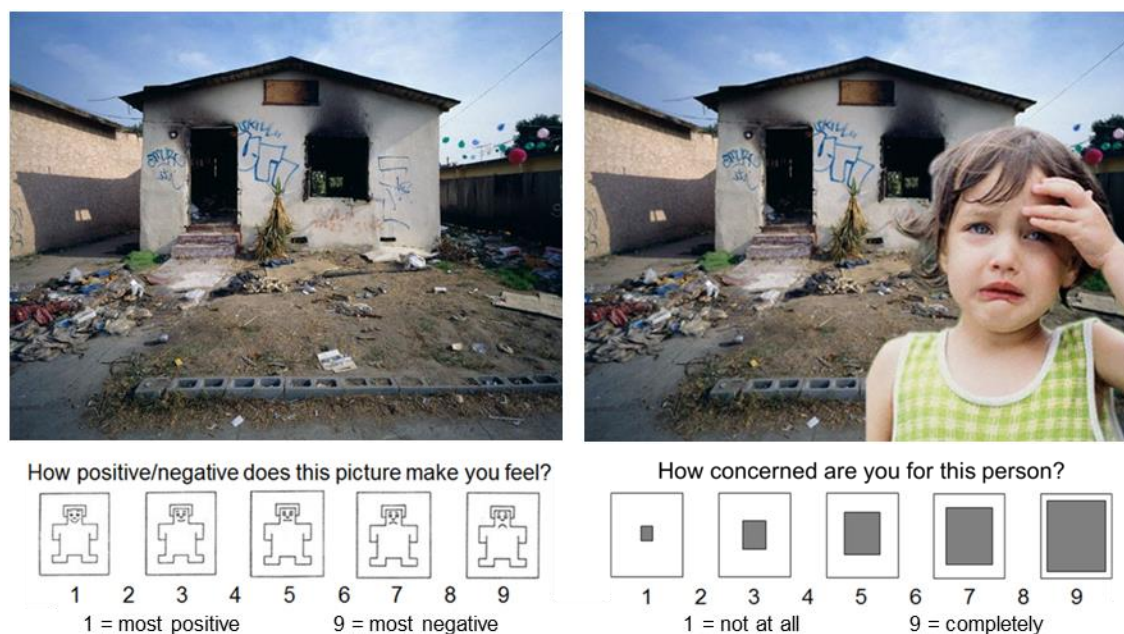


Figure 2.1 The Multifaceted Empathy Test

Example of a negative context-only image with the valence rating question and response scale (left), and the corresponding negative social image with the empathic concern question and response scale (right) taken from the Multifaceted Empathy Test (MET; Dziobek et al., 2008).

Table 2.1: MET measures

Measure	Question	Response
Cognitive Empathy		
Accuracy	How do you think this person is feeling?	Choice from 4 possible mental states
Intensity	How _____ do you think this person feels?	1 = not at all, 9 = completely
Emotional Empathy		
Empathic Concern	How concerned are you for this person? (negative stimuli) How happy are you for this person? (positive stimuli)	1 = not at all, 9 = completely
Affective Sharing		
Intensity	When looking at this picture, does it make YOU feel _____ at all? If so, how _____ do you feel?	1 = not at all, 9 = completely
Valence	How positive or negative does this picture make you feel?	1 = most positive, 9 = most negative
Arousal	How calm or aroused does this picture make you feel?	1 = most calm, 9 = most aroused
Context-Only		
Valence	How positive or negative does this picture make you feel?	1 = most positive, 9 = most negative
Arousal	How calm or aroused does this picture make you feel?	1 = most calm, 9 = most aroused

2.2.2.3 Interpersonal Reactivity Index (IRI; Davis, 1980)

Caregivers of the patients with bvFTD also completed a third-person version of the IRI, a well-validated multidimensional empathy questionnaire (mean scores presented in Table 2.2). The IRI consists of four subscales, each comprised of seven items answered using a 5-point Likert scale ranging from ‘Does not describe him/her well’ to ‘Describes him/her very well’. The subscales of interest for this investigation included the Perspective Taking subscale, which assesses the tendency to spontaneously adopt the perspective of another individual (e.g., ‘I try to look at everybody's side of a disagreement before I make a decision’), and best captures cognitive empathy. In addition, the Empathic Concern subscale evaluates the extent to which someone experiences feelings of concern and sympathy for unfortunate others (e.g., ‘I often have tender, concerned feelings for people less fortunate than me’), and the Personal Distress subscale measures the tendency to experience distress in tense interpersonal situations (e.g., ‘When I see someone who badly needs help in an emergency, I go to pieces’). The Empathic Concern scale in particular is thought to be reflective of emotional empathy, whereas the Personal Distress subscale is believed by some to be a less mature form of emotional empathy akin to emotional contagion (Dziobek et al., 2008; Rankin et al., 2005). All but two of the patients had caregivers complete the IRI, leaving an N of 22 for scores on the Perspective Taking, Empathic Concern, and Personal Distress subscales.

2.2.3 Statistical approach

Chi-square analyses and independent t-tests were conducted to determine whether there were between-groups differences in demographics and/or standardized neuropsychological test performance. Two (group) by two (valence) repeated-measures ANOVAs were utilized to determine whether performance differed between negative and positive stimuli and/or the control group and the patients with bvFTD for each of the cognitive and emotional empathy measures included in the MET. Repeated-measures ANOVAs were also conducted on the valence and arousal ratings provided for the context-only stimuli. Follow-up independent and paired t-tests,

with Bonferroni correction and corrected values according to Levene's Test where appropriate, were conducted to delineate the nature of significant effects. Repeated-measures ANCOVAs were also performed on empathic concern and affective sharing intensity measures of emotional empathy with context-only valence and arousal ratings as covariates to control for effects unrelated to the social content of stimuli.

In addition, correlational analyses were also performed to investigate the association between measures of cognitive and emotional empathy on the MET and corresponding subscales on the IRI in the patients with bvFTD. These analyses included patient MET data from both negative and positive stimuli for the Perspective Taking subscale, and only the negative stimuli for the Empathic Concern and Personal Distress subscales, based on the predominantly negative valence of the items on these subscales of the IRI. Specifically, the relationship between cognitive empathy accuracy and scores on the Perspective Taking subscale of the IRI was examined. Correlational analyses were also performed on empathic concern ratings and affective sharing intensity ratings for negative images with scores on the Empathic Concern subscale of the IRI. Lastly, correlations between affective sharing arousal ratings for negative images and scores on the Personal Distress subscale of the IRI were examined. None of the distributions included in these correlational analyses deviated significantly from normality according to visual inspection of normal Q-Q plots and the Shapiro-Wilk Test (all $p > .05$). Scatter plots for each of these correlations of interest were examined, and Mahalanobis distance values were calculated for each participant in order to detect bivariate outliers [data points with a Mahalanobis distance value greater than the critical chi-square value of 5.99 ($df = 2, p < .05$)]. One outlier was identified as influencing the relationship between scores on the Empathic Concern subscale and both empathic concern ratings and affective sharing intensity ratings for negative stimuli. Thus, correlational analyses were conducted for these variables with this participant's data removed ($N = 21$). Two outliers were also removed from the correlational analysis for Personal Distress and affective sharing arousal ratings for negative images ($N = 20$). No outliers were detected in the Perspective Taking and cognitive empathy accuracy correlational analysis.

Finally, to determine whether impaired cognitive functioning in the patients with bvFTD could account for observed empathy deficits, correlational analyses were conducted between patients' ACE-R total scores and scores on each of the cognitive empathy and emotional

empathy measures for negative and positive stimuli included in the MET. The same outlier criteria as above were used for these analyses.

2.3 Results

2.3.1 Participant demographic and neuropsychological characteristics

Participant demographic and neuropsychological characteristics are presented in Table 2.2. Chi-square analyses revealed no significant difference in sex between bvFTD and control groups. Independent t-tests also demonstrated that groups did not differ significantly in age at testing or years of education. However, patients with bvFTD performed significantly worse than controls on the MMSE and all subtests of the ACE-R. See Table 2.2 for statistical details. In order to confirm that the inclusion of patients with some language deficits who also met diagnostic criteria for semantic dementia ($N = 3$) and PNFA ($N = 2$) did not unduly influence our results, repeated-measures ANOVAs were conducted with these five participants excluded. Results were not substantively different from the whole group analysis. Specifically, the group by valence interactions for cognitive empathy accuracy ($p = .052$) and cognitive empathy intensity ratings ($p = .054$) were marginally significant with the removal of these participants' data, likely consistent with a reduction in power. Because the results remained fundamentally unchanged, data from these patients were included in the analyses.

Table 2.2: Participant demographic and neuropsychological characteristics

Characteristic	Group; mean (SD)		df	p
	Control	bvFTD		
Age at Testing	65.0 (8.5)	64.7 (7.9)	46	> .1
Sex (male:female)	10:14	12:12	1	> .1
Education (years)*	13.5 (3.3)	13.5 (3.1)	45	> .1
Disease Duration (years)	NA	6.0 (3.4)	NA	NA
Mini-Mental State Examination (/30)	28.9 (1.5)	22.0 (5.1)	26.9	< .001
ACE-R [§] Total (/100)	89.3 (7.5)	54.4 (14.5)	33.2	< .001
Attention and Orientation (/18)	17.9 (0.4)	13.8 (3.4)	22.7	< .001
Memory (/26)	20.6 (4.4)	8.0 (4.3)	43	< .001
Fluency (/14)	11.1 (2.0)	4.3 (3.3)	36.9	< .001
Language (/26)	24.9 (1.9)	16.1 (6.3)	26.3	< .001
Visuospatial (/16)	14.8 (1.5)	12.1 (3.4)	31.0	< .005
IRI [☼] Perspective Taking	---	14.1 (4.3)	---	---
Empathic Concern	---	17.8 (4.7)	---	---
Personal Distress	---	18.9 (6.5)	---	---
Total	---	63.0 (14.5)	---	---

SD = standard deviation; *df* = degrees of freedom; bvFTD = behavioural variant frontotemporal dementia; ACE-R = Addenbrooke's Cognitive Examination - Revised

* Education information was available for $N = 23$ control participants

§ ACE-R data were available for $N = 22$ control participants and $N = 23$ patients with bvFTD

☼ IRI data were available for $N = 22$ patients for Perspective Taking, Empathic Concern, and Personal Distress subscales, and $N = 20$ for IRI Total scores

2.3.2 MET

2.3.2.1 Cognitive empathy

Performance on cognitive empathy measures was first examined for both the negative and positive stimuli comparing the healthy control group and the patients with bvFTD. Data are presented in Figure 2.2. Group means and statistical details are presented in Table 2.3. A two (group) by two (valence) repeated-measures ANOVA conducted on cognitive empathy accuracy (i.e., the proportion of mental states correctly identified) demonstrated a main effect of group and valence. Patients with bvFTD ($M = 0.70$, $SD = 0.21$) were less accurate at mental state inference overall relative to healthy controls ($M = 0.95$, $SD = 0.04$), and individuals across groups were less accurate at inferring the mental states of people in negative images ($M = 0.79$, $SD = 0.23$)

compared to positive images ($M = 0.89$, $SD = 0.17$). A group by valence interaction was also apparent, and separate independent t-tests with Bonferroni and Levene's Test corrected p values were conducted for negative and positive stimuli to elucidate this. These demonstrated that patients with bvFTD were less accurate at inferring how the people were feeling in both the negative [$t(26.0) = -5.73$, $p < .001$] and positive [$t(25.5) = -4.40$, $p < .001$] images relative to controls. Thus, patients with bvFTD demonstrated a cognitive empathy deficit for both negative and positive stimuli. Paired t-tests conducted in each of the groups revealed that cognitive empathy accuracy was significantly lower for negative images compared to positive images in the bvFTD group [$t(23) = -4.28$, $p < .001$], as well as the control group [$t(23) = -2.58$, $p < .05$]. However, the interaction appears to be driven by the fact that the differential effect of negative versus positive stimuli is greater in patients than controls (Figure 2.2). A second repeated-measures ANOVA for cognitive empathy intensity ratings unveiled a main effect of valence, but no significant effect of group. Across groups, individuals provided lower intensity ratings for the feelings exemplified in negative images ($M = 7.81$, $SD = 1.3$) in comparison to positive images ($M = 8.11$, $SD = 1.3$). A group by valence interaction was also identified. Follow-up independent t-tests revealed that patients with bvFTD provided significantly lower intensity ratings for the mental states exemplified in the negative images relative to controls [$t(27.3) = -2.46$, $p < .05$], whereas intensity ratings did not differ significantly between the groups for positive stimuli [$t(46) = -0.66$, $p > .1$]. Thus, patients with bvFTD provided lower intensity ratings for negative, but not positive, mental states depicted in comparison to controls.

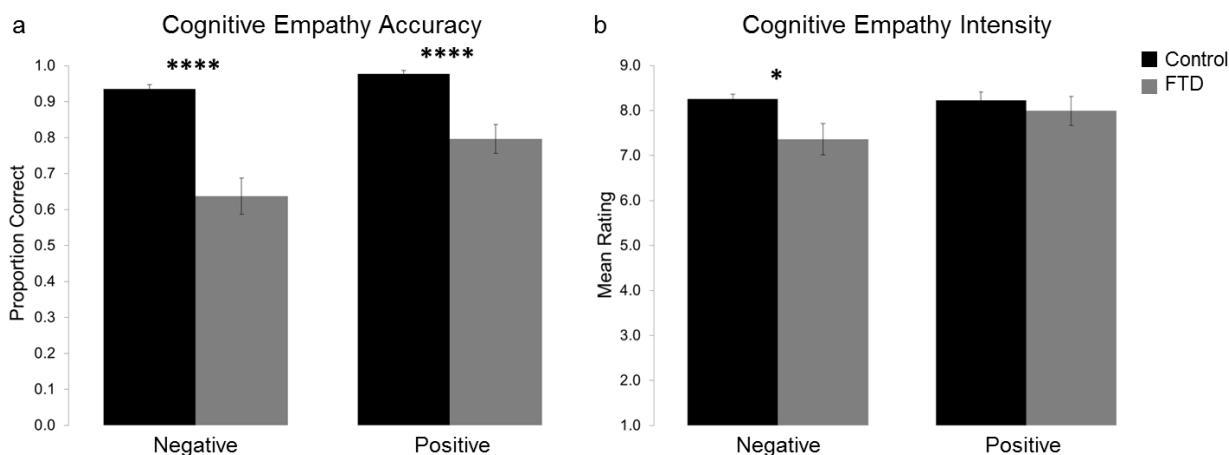


Figure 2.2 Cognitive empathy results

Mean cognitive empathy scores in control and bvFTD groups by stimuli valence. (a) Mean proportion of mental states correctly identified for the negative and positive social stimuli. (b) Mean ratings of feeling intensity for the mental states exemplified in the negative and positive social images. Error bars represent standard errors. Asterisks indicate a significant difference in accuracy, * $p < .05$, **** $p < .001$.

2.3.2.2 Emotional empathy

Emotional empathy data are presented in Figure 2.3. See Table 2.3 for group means and statistical details. Repeated-measures ANOVAs were also conducted to determine whether performance on measures of empathic concern differed as a function of group for negative images (when asked, ‘How concerned are you for this person?’) or positive images (when asked, ‘How happy are you for this person?’). A main effect of valence was apparent for empathic concern ratings, with participants providing lower ratings for negative images ($M = 6.73$, $SD = 1.4$) compared to positive images ($M = 7.47$, $SD = 1.5$). However, the effect of group was non-significant, and there was no significant group by valence interaction. Thus, interestingly patients with bvFTD were found to endorse similar levels of concern as controls for people in negative images, and levels of happiness for those in positive images.

With regard to measures of affective sharing, the repeated-measures ANOVA performed on affective sharing intensity ratings (e.g., when asked, ‘When looking at this picture, does it make YOU feel excited at all? If so, how excited do you feel?’) revealed a main effect of valence, though the effect of group was not significant. Participants reported a lower degree of shared feeling intensity for negative stimuli ($M = 5.47$, $SD = 1.8$) compared to positive stimuli ($M = 6.63$, $SD = 1.5$). There was also a group by valence interaction. Whereas, the patients with bvFTD shared the feelings of people in the negative images to a lesser degree than controls [$t(35.2) = -2.11$, $p = .084$], there was no evidence that the two groups differed in ratings of shared feeling intensity for positive stimuli [$t(39.0) = 0.73$, $p > .1$]. Thus, patients with bvFTD showed diminished levels of affective sharing intensity for negative, but not positive, stimuli relative to controls.

Examining affective sharing further, valence ratings (i.e., how positive or negative a stimulus made the participant feel), demonstrated main effects of group and valence. Patients with bvFTD ($M = 4.34$, $SD = 1.6$) provided lower (i.e., more positive) valence ratings overall relative to controls ($M = 5.16$, $SD = 0.59$), and ratings were significantly lower for positive images ($M = 2.27$, $SD = 1.2$) compared to negative images ($M = 6.34$, $SD = 1.7$), as expected. A group by valence interaction was also apparent. To delineate the observed interaction, separate independent t-tests were undertaken for each valence. These revealed that patients with bvFTD rated negative stimuli as making them feel less negative than controls [$t(32.7) = -3.00$, $p < .05$], though there was no significant difference between groups for ratings of how the positive stimuli made them feel [$t(46) = 0.041$, $p > .1$]. Therefore, patients with bvFTD felt less negative in response to negative stimuli relative to controls, but showed no significant difference in the feelings elicited by positive stimuli.

For arousal ratings, the final measure of affective sharing (i.e., how calm or aroused a stimulus made the participant feel), there was a main effect of valence, but no significant effect of group. Participants rated negative stimuli ($M = 5.78$, $SD = 1.5$) as making them feel more aroused than positive stimuli ($M = 3.23$, $SD = 1.6$). A group by valence interaction was also found for arousal ratings. Independent t-tests demonstrated that the patients with bvFTD provided significantly lower arousal ratings than controls for negative images [$t(38.0) = -3.08$, $p < .01$], but there was no significant difference in arousal ratings between groups for positive

images [$t(37.2) = 1.74, p > .1$]. Thus, patients with bvFTD expressed lower levels of arousal in response to negative, but not positive, stimuli in comparison to controls.

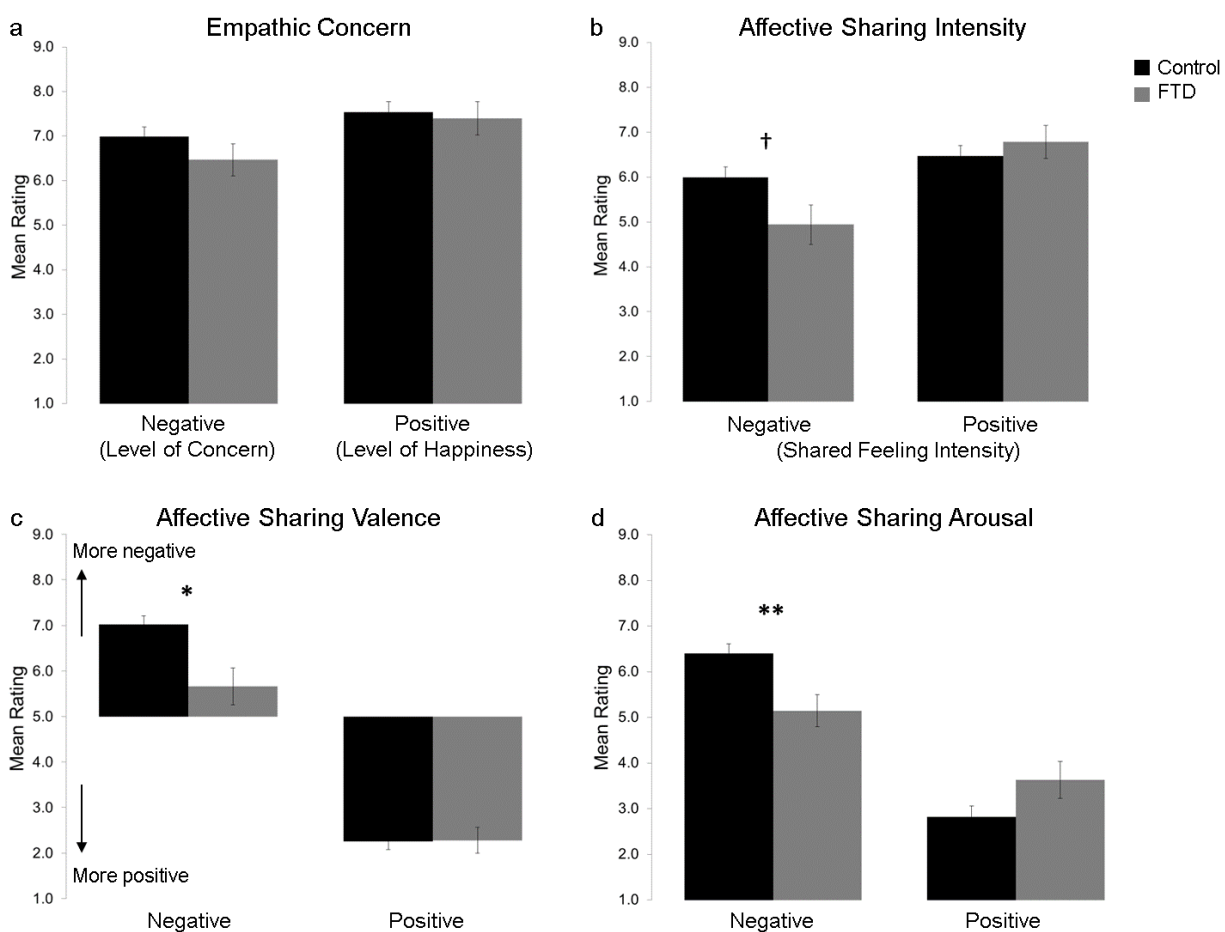


Figure 2.3 Emotional empathy results

Mean emotional empathy ratings in control and bvFTD groups by stimuli valence. (a) Mean ratings of concern (for negative stimuli) and happiness (for positive stimuli) for the individuals in the social images. (b) Mean ratings of the degree to which participants shared the feelings of those in the negative and positive social stimuli. (c) Mean ratings of how positive or negative the image made participants feel (1 = most positive, 9 = most negative) for negative and positive social stimuli. (d) Mean ratings of how calm or aroused the image made participants feel (1 = most calm, 9 = most aroused) for negative and positive social stimuli. Error bars represent

standard errors. Asterisks indicate a significant difference in accuracy, * $p < .05$, ** $p < .01$, † $p < .05$ uncorrected ($p = .084$ with Bonferroni correction).

2.3.2.3 Context-only stimuli

In order to determine whether the impairments demonstrated by the patients with bvFTD were specific to social stimuli or represented a more generalized processing difference, repeated-measures ANOVAs were also conducted on valence and arousal ratings for the negative and positive context-only stimuli. Data for context-only stimuli are presented in Figure 2.4. Group means and statistical details are presented in Table 2.3. As with the social stimuli containing people, for valence ratings of context-only stimuli there were main effects of group and valence. Patients with bvFTD ($M = 3.76$, $SD = 1.4$) provided lower (i.e., more positive) ratings than controls ($M = 4.61$, $SD = 0.64$) across valences, and participants across groups provided higher (i.e., more negative) ratings for negative stimuli ($M = 5.29$, $SD = 1.5$) in comparison to positive stimuli ($M = 2.47$, $SD = 1.0$), as expected. A group by valence interaction was also identified. Independent t-tests for each valence demonstrated that the patients with bvFTD rated negative context-only stimuli as making them feel significantly less negative than controls [$t(33.3) = -3.45$, $p < .005$]. Interestingly, patients actually rated the negative context-only stimuli as making them feel slightly positive on average. There was no significant difference in valence ratings for positive context-only stimuli between the patients and controls [$t(46) = -0.15$, $p > .1$]. Lastly, for arousal ratings of context-only images, there was a main effect of valence, but no significant effect of group. Participants rated positive context-only images ($M = 3.06$, $SD = 1.3$) as less arousing than negative context-only images ($M = 5.07$, $SD = 1.5$). A group by valence interaction was also apparent. Separate independent t-tests for each valence suggested that this interaction was driven by a trend of patients with bvFTD providing lower arousal ratings for negative context-only stimuli relative to controls, though this trend did not survive Bonferroni correction [$t(37.3) = -1.95$, $p = .118$]. There was no indication of a difference in arousal ratings for positive context-only stimuli between the patients with bvFTD and the controls [$t(46) = 0.93$, $p > .1$]. Thus, patients with bvFTD provided ratings indicative of decreased emotional responding specifically to negative context-only stimuli relative to controls.

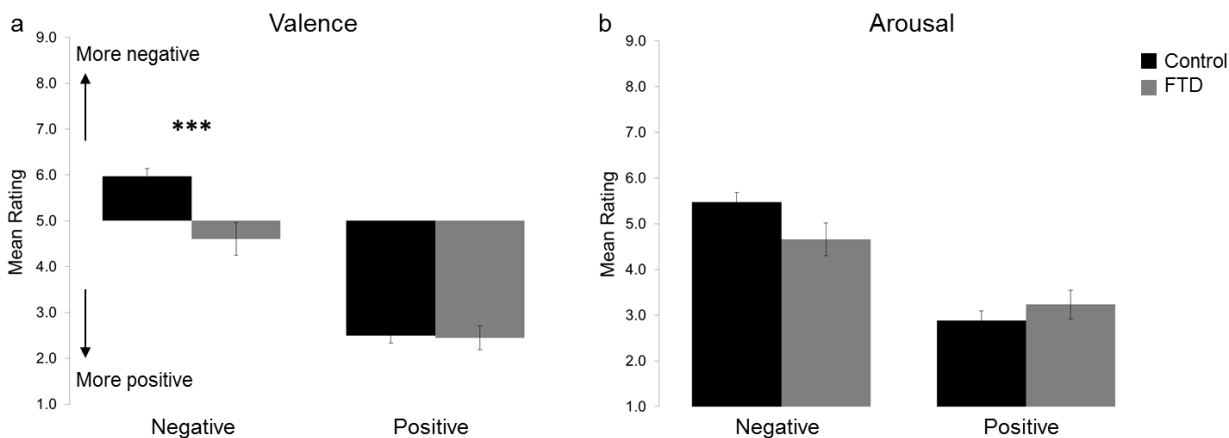


Figure 2.4 Context-only results

Mean ratings for context-only stimuli in control and bvFTD groups by stimuli valence. (a) Mean ratings of how positive or negative the image made participants feel (1 = most positive, 9 = most negative) for negative and positive context-only stimuli. (b) Mean ratings of how calm or aroused the image made participants feel (1 = most calm, 9 = most aroused) for negative and positive context-only stimuli. Error bars represent standard errors. Asterisks indicate a significant difference in accuracy, *** $p < .005$.

Table 2.3: Group means and statistical details for MET measure main effects and interactions

Measure	Negative Stimuli; mean (SD)		Positive Stimuli; mean (SD)		Effect ($df = 46$)					
	Control	bvFTD	Control	bvFTD	Group		Valence		Group X Valence	
					F	p	F	p	F	p
Cognitive Empathy										
Accuracy (%)	93 (6.3)	64 (25)	98 (4.6)	80 (20)	32.2	< .001	24.6	< .001	8.28	< .01
Intensity	8.26 (0.52)	7.36 (1.7)	8.23 (0.90)	7.99 (1.6)	2.90	.096	4.11	< .05	4.80	< .05
Emotional Empathy										
Empathic Concern	6.99 (1.0)	6.47 (1.8)	7.53 (1.2)	7.40 (1.8)	0.699	> .1	17.4	< .001	1.19	> .1
Affective Sharing										
Intensity	5.99 (1.2)	4.94 (2.1)	6.47 (1.1)	6.79 (1.8)	0.794	> .1	26.6	< .001	9.26	< .005
Valence	7.02 (0.94)	5.66 (2.0)	2.26 (0.92)	2.28 (1.4)	4.24	< .05	311	< .001	8.82	< .01
Arousal	6.40 (1.0)	5.15 (1.7)	2.82 (1.2)	3.63 (2.0)	0.412	> .1	93.2	< .001	15.4	< .001
Context-Only										
Valence	5.97 (0.85)	4.60 (1.7)	2.49 (0.78)	2.44 (1.3)	5.72	< .05	218	< .001	11.9	< .005
Arousal	5.47 (1.0)	4.66 (1.8)	2.88 (1.1)	3.24 (1.5)	0.398	> .1	137	< .001	11.6	< .005

SD = standard deviation; df = degrees of freedom; bvFTD = behavioural variant frontotemporal dementia

2.3.3 Controlling for context-only effects

To determine whether the emotional empathy deficits observed could be driven by abnormalities in patient ratings for the context-only, non-social stimuli, separate repeated-measures ANCOVAs with context-only ratings were conducted on the indices of emotional empathy. Interestingly, these analyses indicated that abnormalities in context-only valence ratings impacted ratings of shared feeling intensity for negative images. Thus, we cannot conclude whether the lower degree of affective sharing intensity (i.e., shared feeling intensity) for people in negative images expressed by patients with bvFTD was driven mainly by the contextual aspects of the stimuli, or by responses specific to the depicted persons.

2.3.4 Correlational analyses

Correlational analyses were performed to investigate the relationship between measures of cognitive and emotional empathy on the performance-based MET and caregiver-completed IRI in patients with bvFTD. As mentioned, the negative valence of most items on the Empathic Concern and Personal Distress subscales of the IRI prompted the inclusion of MET emotional empathy data for the negative stimuli only. Correlational analyses between cognitive empathy accuracy on the MET and scores on the Perspective Taking subscale of the IRI revealed no significant association between the two measures ($r = .205, p > .1$). However, a positive correlation was identified between empathic concern ratings for negative images and scores on the Empathic Concern subscale ($r = .438, p < .05$; Figure 2.5a). A trend of a positive relationship was also evident between affective sharing intensity ratings for negative images and scores on the Empathic Concern subscale ($r = .415, p = .061$; Figure 2.5b). Finally, there was no significant correlation between patients' affective sharing arousal ratings for negative stimuli and their scores on the Personal Distress subscale of the IRI ($r = .091, p > .1$). Thus, within the bvFTD group, a positive association was apparent between measures of emotional empathy, but not cognitive empathy, on the MET and IRI.

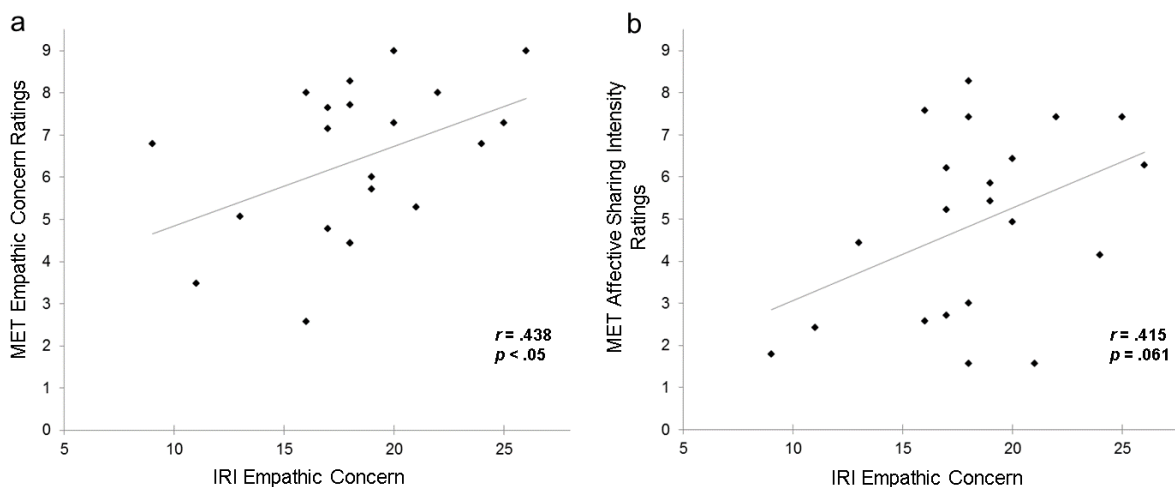


Figure 2.5 Correlational analyses

Correlation between Multifaceted Empathy Test (MET) and Interpersonal Reactivity Index (IRI) measures of emotional empathy. Plots with best-fitting regression lines showing (a) MET empathic concern ratings for negative stimuli (i.e., level of concern for people) and (b) MET affective sharing intensity ratings for negative stimuli (i.e., level of shared emotional experience) as a function of scores on the Empathic Concern subscale of the IRI for patients with bvFTD.

In order to investigate the influence of cognitive functioning deficits on MET empathic performance, correlational analyses were also performed using ACE-R total scores and scores on each of the cognitive empathy and emotional empathy measures for negative and positive stimuli included in the MET, for the patients with bvFTD. Performance on several of the MET measures was found to be positively associated with ACE-R total scores (Table 2.4). Correlational analyses reported here were performed using ACE-R total scores as we felt attention, executive functioning, language, and visuospatial abilities might all be engaged to some extent by the MET.

Table 2.4: Correlational analyses between ACE-R total scores and MET measures of cognitive and emotional empathy in patients with bvFTD

Measure	Valence	<i>p</i>	<i>r</i>
Cognitive Empathy			
Accuracy	Negative	> .1	.357
	Positive	.047	.428
Intensity	Negative	> .1	.020
	Positive	> .1	-.321
Emotional Empathy			
Empathic Concern			
	Negative	> .1	.074
	Positive	> .1	.094
Affective Sharing			
Intensity	Negative	.065	.400
	Positive	> .1	.059
Valence	Negative	.050	.434
	Positive	> .1	-.005
Arousal	Negative	.054	.417
	Positive	> .1	.279

2.3.5 Summary

Overall, patients with bvFTD performed worse than controls at mental state inference for both negative and positive images. They also expressed sharing the emotional experience of others to a lesser degree, less negative emotional reactions, and lower levels of arousal for negative, but not positive, social stimuli. Additionally, patients demonstrated diminished emotional responses to negative, but not positive, non-social context-only stimuli relative to controls. Covariate analyses suggested that impaired encoding of negative contextual cues could contribute to the observed emotional empathy deficit. Lastly, measures of emotional empathy on the MET and IRI were found to be positively correlated within the bvFTD group, and cognitive functioning was associated with several of the MET measures.

2.4 Discussion

Previous investigations of empathic capacity in patients with bvFTD have demonstrated deficits in both cognitive empathy (i.e., the ability to adopt and understand the perspective of another individual) and emotional empathy (i.e., the tendency to share and react affectively to another's emotional experience). However, the present investigation utilizing the MET represents the first time that empathic responding to negative versus positive mental states has been evaluated in patients with FTD. Further, we assessed emotional empathy in this patient population using a performance-based measure, as opposed to caregiver or clinician reports. Patients with bvFTD presented with a deficit in inferring both negative and positive mental states, indicative of a global deficit in cognitive empathy. Deficient affective sharing for negative experiences was also demonstrated in patients with bvFTD, by way of lower levels of shared emotional experience, less negative emotional reactions, and decreased arousal to negative social stimuli. Patients with bvFTD also reported less negative emotional reactions to negative context-only stimuli relative to healthy controls. Strikingly, there was no evidence of impairment in emotional empathy for positive social stimuli or emotional responsivity for positive context-only stimuli in patients with bvFTD. They expressed similar levels of shared feeling intensity, valence, and arousal for positive social stimuli in comparison to controls, and provided similar valence and arousal ratings for positive context-only stimuli.

As predicted, patients with bvFTD demonstrated a deficit in cognitive empathy accuracy in comparison to healthy controls. This impairment has been well established in the literature using theory of mind tasks (for reviews see Henry, Phillips, & von Hippel, 2014; Poletti, Enrici, & Adenzato, 2012) and the Perspective Taking subscale of the IRI (Eslinger et al., 2011; Rankin et al., 2006; Rankin et al., 2005). Though patients with bvFTD have shown deficits on theory of mind tasks that include both negative and positive stimuli such as the Reading the Mind in the Eyes task (Couto et al., 2013; Gregory et al., 2002; Torralva et al., 2007), their reported performance has not been parsed apart by valence. The MET includes a performance-based measure of cognitive empathy, similar to a theory of mind task, but it is scored in a manner that distinguishes between responses to negative versus positive mental states. Patients with bvFTD were significantly worse at inferring the mental states of people (i.e., exhibited lower cognitive empathy accuracy) for both the negative and positive images. Thus, we provide evidence that

patients with bvFTD demonstrate a cognitive empathy impairment for both negative and positive states. Nevertheless, patients with bvFTD appeared to exhibit a more pronounced deficit for inferring negative compared to positive mental states, as anticipated. Although controls showed a similar pattern, the significant interaction was driven by a greater differential effect of valence in the patient group relative to the control group. However, this interaction should be interpreted with caution. Because the controls performed at close to ceiling for positive stimuli, the differential effect for this group may have been constrained by the limited range of scores available. As well, it is possible that this disparity could be due to increased difficulty of recognizing negative mental states, as healthy individuals have more difficulty recognizing negative emotions (Russell, 1994). Regardless, a more pronounced deficit for inferring negative mental states in patients with bvFTD is of interest because there is some evidence of a selective impairment in recognizing negative, but not positive, emotional expressions in patients with bvFTD (Fernandez-Duque & Black, 2005; Kipps, Mioshi, et al., 2009; Kumfor et al., 2011; Lavenu et al., 1999; Lough et al., 2006). Further, patients with bvFTD were found to provide lower intensity ratings for the mental states portrayed in negative images relative to controls (cognitive empathy intensity), while intensity ratings did not differ between groups for positive mental states. Thus, the present results indicated that patients with bvFTD have a global cognitive empathy deficit, which may be more pronounced for negative stimuli.

Patients with bvFTD also exhibited an emotional empathy impairment relative to controls, as reflected by indices of affective sharing, selectively for negative experiences. Though this has been subjectively demonstrated by way of caregiver ratings on the Empathic Concern subscale of the IRI (Eslinger et al., 2011; Lough et al., 2006; Rankin et al., 2006) and case descriptions (Lough et al., 2001; Snowden et al., 2001; Thibodeau & Miller, 2013), far less work has been done examining deficiencies in emotional empathic responses using a behavioural measure in this patient population. However, it should be noted that aspects of emotional reactivity have been investigated in patients with bvFTD in response to emotion-eliciting videos. Our findings fall in line with demonstrations of diminished facial displays of emotion, subjective emotional experience, and physiological responding while viewing a disgust-eliciting film in patients with bvFTD relative to controls (Eckart et al., 2012). Very recently, patients with bvFTD have been found to rate negative emotional stimuli containing people as less negative than matched controls, whereas their valence ratings of positive and neutral stimuli did not differ

significantly from controls (St. Jacques et al., 2014). We have replicated these valence-specific findings, and also provide further insight into the influence of a general deficit in emotional encoding through the inclusion of both stimuli containing people and context-only stimuli.

It has been suggested that emotional empathy not only involves the shared experience of emotional states, but also the translation and comprehension of emotional expressions (Blair, 2013). Indeed, brain regions implicated in processing and/or recognizing emotional expressions are also thought to be involved in emotional empathy (Blair, 2005). The more pronounced deficit in bvFTD patients' empathic abilities for negative mental states observed on the MET thus is consistent with reports of impaired recognition of negative emotional expressions, but intact recognition of happy faces, in patients with bvFTD (Fernandez-Duque & Black, 2005; Kipps, Mioshi, et al., 2009; Kumfor et al., 2011; Lavenu et al., 1999; Lough et al., 2006; but see also Diehl-Schmid et al., 2007; Keane, Calder, Hodges, & Young, 2002; Snowden et al., 2008). It should be noted that increased difficulty recognizing negative emotions is also apparent in the healthy population (Russell, 1994), such that task difficulty may contribute to our observed effects. However, preservation of happiness recognition has been demonstrated in patients with bvFTD even when using morphed facial expressions to increase task sensitivity (Lough et al., 2006). Furthermore, in the context of the current study, unlike facial expression recognition paradigms where there is a correct and incorrect answer, it is more difficult to explain a difference in levels of shared emotional experience or arousal with respect to a task difficulty effect. These are subjective ratings of emotional reactions and experience, and though some responses may be conventionally more appropriate, none are strictly incorrect. These deficits in emotion recognition and affective sharing for negative stimuli may be the result of greater atrophy in regions involved in the processing and recognition of negative emotions (Kumfor & Piguet, 2012). More specifically, negative emotions such as fear and disgust appear to have more focal representation in the brain, such that lesions to specific regions can result in relatively selective recognition deficits for these expressions (Adolphs et al., 1999; Calder, Keane, Manes, Antoun, & Young, 2000; Hennenlotter et al., 2004). Abnormalities in similar regions, including the amygdala and insula, have also been associated with deficient processing of negative emotional expressions in patients with bvFTD (Couto et al., 2013; Kipps, Nestor, Acosta-Cabrero, Arnold, & Hodges, 2009; Kumfor, Irish, Hodges, & Piguet, 2013; Moll et al., 2011; Virani, Jesso, Kertesz, Mitchell, & Finger, 2013). In contrast, happiness recognition tends to be

well-preserved across patient populations, including those with lesions and developmental disorders. This suggests that the processing and recognition of happy expressions may be represented more diffusely (Breiter et al., 1996; Fusar-Poli et al., 2009; O'Doherty et al., 2003; Phillips et al., 1998).

The MET includes both images with a context alone and images with emotional individuals embedded in the same context. Thus, it allows for the discrimination between affective responses to emotionally charged context-only, non-social and social stimuli (Dziobek et al., 2008). In addition to the empathy deficits observed for social stimuli, patients showed decreased emotional responsivity for negative, but not positive, non-social stimuli. Notably, these findings are not indicative of a positivity bias, as patients did not rate positive stimuli more positively than controls, and neither of the groups performed at ceiling. It could be argued that the MET context-only stimuli include images with an implied social component (e.g., a crashed car, an empty grave). Thus, interpreting these images as negative may be facilitated by an understanding of the social ramifications of these contexts. However, at least one other study has demonstrated reduced responding in patients with FTD to aversive non-social stimuli (i.e., bursts of white noise; Hofer et al., 2008). Further, our covariate analyses controlling for context-only valence ratings indicate that deficient encoding of negative contextual cues may contribute to the emotional empathy deficits observed in patients with bvFTD. Impaired performance on affective sharing measures for negative stimuli, but not empathic concern, in patients with bvFTD does suggest that impaired processing of negative contextual cues is not solely responsible for the demonstrated emotional empathy deficits. In relation to this, it is interesting to note the divergent effects obtained for empathic concern versus affective sharing measures. Patients with bvFTD did not show significant differences in their endorsements of empathic concern (i.e., level of concern for people in negative images, or level of happiness for people in positive images), but exhibited impaired affective sharing for negative experiences (e.g., reduced shared feelings) relative to controls. Affective sharing measures could be considered indirect or implicit measures of emotional empathy, as they query about emotional responses self-referentially, without actually referring to the people in the image (Dziobek et al., 2008). Alternatively, empathic concern is a more direct or explicit index of emotional empathy in that it blatantly asks how the participant is feeling for the people in the picture. In this way, affective sharing may be a more sensitive index of the difficulties faced by patients with bvFTD, as daily social interactions tend

not to be structured or guided. Similarly, patients may be better able to discern what a socially appropriate response is for the more explicit empathic concern index than for the affective sharing measures of emotional empathy. Additionally, affective sharing likely better captures emotional contagion, providing insight into the specific mechanisms that could be responsible for emotional empathy deficits in bvFTD. Deficient responding to these affective sharing indices for negative stimuli therefore supports the notion that the spontaneous expression of empathy is blunted in bvFTD.

Whether cognitive functioning was related to performance on the MET in patients with bvFTD is also of interest. Correlational analyses between ACE-R total scores and MET measures revealed a positive association between cognitive empathy accuracy for positive stimuli and ACE-R scores, as well as marginally significant positive correlations between ACE-R scores and affective sharing measures (intensity, valence, and arousal) for negative stimuli. The correlations with ACE-R total scores broadly coincide with results from a previous study demonstrating an association between cognitive functioning and measures of both cognitive and emotional empathy in patients with bvFTD (Eslinger et al., 2011). Similarly, positive correlations have been identified between measures of theory of mind and empathy, and executive resources in patients with FTD with social and executive impairments (Eslinger et al., 2007). Deficits in observable social behaviour in patients with bvFTD have also been found to be associated with measures of executive functioning (Mendez et al., 2014). Accordingly, it has been proposed that deficits in cognitive and social functioning in patients with bvFTD may be critically linked, and that the deterioration of both social knowledge and executive resources contribute to empathy impairments (Eslinger et al., 2011; Eslinger et al., 2007). Executive dysfunction and behavioural abnormalities in patients with FTD have been correlated with diminished activity in partially overlapping brain areas, including regions implicated in theory of mind or cognitive empathy (Raczka et al., 2010). This may help to explain why some behavioural deficits are linked to executive functioning in FTD. The present results indicate a relationship between cognitive functioning and MET performance, though the lack of strength and specificity of correlations does not suggest that cognitive demand is solely responsible for the observed deficits.

As mentioned, the caregiver version of the IRI has been utilized in many previous investigations to evaluate both cognitive and emotional empathy in bvFTD. Because the MET

also evaluates aspects of cognitive and emotional empathy, and has been validated using the IRI in healthy individuals (Dziobek et al., 2008; Hysek et al., 2013), we expected to find a correlation between measures on the MET and the related IRI subscales. Though the measures of cognitive empathy on these metrics were not significantly associated, the MET and IRI measures of emotional empathy were found to be correlated within the bvFTD group. Thus, we provide further construct validation in FTD for measures of emotional empathy on the MET, consistent with the relationships that have been demonstrated between the MET and the IRI in the healthy population (Dziobek et al., 2008). The lack of a correlation for cognitive empathy as assessed on the MET and Perspective Taking on the IRI is in line with prior results in healthy adults which did not demonstrate a significant correlation between these two scales (Dziobek et al., 2008; Hysek et al., 2013). It should also be noted that though IRI data was not collected for controls, comparisons between ratings for our bvFTD and control groups could have provided insight into the consistency of deficits demonstrated in bvFTD. Collecting IRI data for control participants might have also served to strengthen the MET and IRI correlations.

This lack of an association for cognitive empathy measures on the MET and IRI, as well as the absence of stronger correlations between the emotional empathy scales, likely reflects the differential behaviours captured by the two measures. The caregivers complete the IRI based on their observations of the naturalistic everyday behaviour of the patient, while patient performance may be optimized for behavioural measures in the clinic where motivation is often high and distractors are limited (Mioshi, Kipps, & Hodges, 2009). Further, the components of cognitive and/or emotional empathy assessed via the items on the IRI likely differ from the MET. For example, items on the Perspective Taking subscale of the IRI focus on the history of attempts to consider another's mental state, such as 'I sometimes try to understand my friends better by imagining how things look from their perspective', and the majority of them contain the word 'try' (Davis, 1980). In contrast, the cognitive empathy accuracy measure on the MET requires the participant to actively infer the mental states of other individuals (i.e., explicit mental state inference performance). While these both likely contribute to the empathic behaviour exhibited by an individual, the lack of correlation may reflect the distinct components indexed by each measure. Our results indicate that treatment studies or interventions targeting empathy and related behaviours would benefit from inclusion of both the MET and IRI, as performance-based measures may be more sensitive to changes over time in emotional capacity.

While the IRI captures functionally relevant changes in empathy that directly impact the caregiver-patient dyad in FTD, some behavioural questionnaire measures show improvement in scores despite disease progression (Chow et al., 2012; Knopman et al., 2008). In such a situation, complimentary performance-based measures may help to clarify the basis for such behavioural changes. Based on our findings, emotional empathy as assessed by the MET affective sharing intensity ratings may serve as the best outcome measure of performance-based emotional empathy in patients with bvFTD.

Importantly, the MET is a newer measure of empathic performance which has not been utilized previously in patients with FTD. As such, further use of the MET in independent cohorts is necessary to replicate findings and determine the sensitivity and specificity of its measures of cognitive and emotional empathy. Notably, though performance-based measures like the MET arguably allow for a more direct assessment of empathic abilities, they are still susceptible to the influence of bias such as the potential conforming of answers to socially desirable responses. Thus, it is possible that individuals could use cognitive strategies to provide these ratings. Future studies would benefit from inclusion of physiological measures during the task to confirm that emotional empathy ratings reflect genuine changes in affective responding. Lastly, it is important to keep in mind that though evidence supports the existence of dissociable cognitive and emotional facets of empathy, it is likely that these aspects work together in daily life and both contribute to typical empathic experience (Shamay-Tsoory, 2011).

In summary, the use of the MET (Dziobek et al., 2008) to index cognitive and emotional empathy in patients with bvFTD uniquely allowed for the discrimination of empathic responses to negative versus positive stimuli, as well as the behavioural assessment of emotional empathy. Overall, using a performance-based measure we demonstrate deficits in both cognitive and emotional empathy in patients with bvFTD, particularly for negative social stimuli, as well as diminished emotional responses to negative non-social stimuli. A generalized deficit in emotional responding to negative stimuli may therefore contribute to the emotional empathy impairments associated with bvFTD, though further research regarding emotional reactivity to non-social stimuli in patients with bvFTD is necessary to elucidate this. The present work may serve to highlight potential treatment targets and a means to assess the impact of novel therapies on social and emotional impairment in bvFTD. Specifically, the MET may prove useful as a

performance-based measure to index aspects of cognitive and emotional empathy in patients with bvFTD.

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Chapter 3

3 Distinguishing the Relationship Between Different Aspects of Empathic Responding as a Function of Psychopathic, Autistic, and Anxious Traits²

Abstract

Although deficits in cognitive and emotional empathy are associated with specific developmental and neurological disorders, such as autism and psychopathy, little is known about the relationship between individual differences in psychopathic, autistic, and anxious traits, and behavioural measures of cognitive empathy, empathic concern, and affective sharing. Particularly, investigations of empathy rarely consider anxiety, or distinguish between different components of emotional empathy. Presently, healthy adults completed trait questionnaire measures and the Multifaceted Empathy Test, a performance-based task tapping cognitive empathy and multiple aspects of emotional empathy elicited by emotionally-charged realistic images. Heightened coldhearted psychopathic traits were associated with reduced empathic concern and affective sharing in response to affective images, and were unrelated to cognitive empathy performance. As expected, autistic traits were not associated with emotional empathy. Increased trait anxiety was linked to greater affective sharing, and arousal in particular, but this was driven by arousal elicited by contextual rather than social aspects of the stimuli. Thus, while coldhearted psychopathic traits appear to disrupt empathic processes thought to motivate altruistic behaviours, trait anxiety may influence subjective affective experience without instilling greater emotional empathy.

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3.1 Introduction

Empathy, the comprehension, identification, and/or vicarious experience elicited by another individual's state, plays a critical role in human social interaction. Accordingly, impaired empathy is a key feature of many debilitating developmental, neurological, and personality disorders. Empathy is largely considered to be a multidimensional construct that includes both cognitive and emotional facets (Blair, 2005; Shamay-Tsoory, 2011). Although the purported number of distinct facets of empathy varies, it has been proposed that empathy is comprised of cognitive empathy, empathic concern, and affective sharing components (Bernhardt & Singer, 2012; Decety & Cowell, 2014; Preston & de Waal, 2002; Zaki & Ochsner, 2012). Cognitive empathy, often used interchangeably with theory of mind (Blair, 2005; Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004), refers to the ability to adopt another individual's perspective, and thereby infer their mental state. Whereas empathic concern refers to the motivation to care for another's welfare, affective sharing relates to the capacity to share the emotional experience of another person. Thus, affective sharing involves an isomorphic emotional response to another individual, while empathic concern may not. Notably, the dissociation of cognitive and emotional empathy is supported by behavioural (Lockwood, Bird, Bridge, & Viding, 2013), lesion (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009), and functional imaging (Fan, Duncan, de Greck, & Northoff, 2011) studies, but less is known about the dissociability of empathic concern versus affective sharing. Indeed, most investigations do not distinguish between these two putative components, instead using "emotional empathy" to refer to either.

Importantly, distinct facets of empathy seem to be differentially affected in particular disorders. Specifically, psychopathic tendencies are typically linked to impaired emotional empathy, but intact cognitive empathy. In contrast, autism spectrum disorder has been associated with deficits in cognitive but not emotional empathy in some studies. This double dissociation has been demonstrated behaviourally in youths with autism spectrum disorder versus psychopathic tendencies (Jones, Happe, Gilbert, Burnett, & Viding, 2010; Schwenck et al., 2012). Further, evidence for deficient emotional empathy in adults with psychopathy and youths with psychopathic tendencies has been inferred from demonstrations of impaired emotion recognition (Fairchild, Van Goozen, Calder, Stollery, & Goodyer, 2009; Hastings, Tangney, & Stuewig, 2008), dampened electrodermal responding to distress cues (Blair, 1999; Blair, Jones,

Clark, & Smith, 1997), and abnormal BOLD response to emotional stimuli in affect-related brain regions (Decety, Skelly, Yoder, & Kiehl, 2014; Marsh et al., 2008). Cognitive empathy impairments in individuals with autism spectrum disorder have been demonstrated using false belief paradigms (Baron-Cohen, Leslie, & Frith, 1985) and mental state inference tasks (Abell, Happe, & Frith, 2000; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Happe, 1994). In addition, adults with autism show a cognitive empathy deficit but intact empathic concern and affective arousal on the Multifaceted Empathy Test (Dziobek et al., 2008). However, it should be noted that there have been demonstrations of decreased emotional empathy scores on questionnaire measures in patients with autism spectrum disorder compared to healthy controls (Grove, Baillie, Allison, Baron-Cohen, & Hoekstra, 2014; Mathersul, McDonald, & Rushby, 2013b, 2013d; Shamay-Tsoory, Tomer, Yaniv, & Aharon-Peretz, 2002), as well as atypical autonomic arousal in response to face stimuli (Mathersul, McDonald, & Rushby, 2013a, 2013c). With regard to emotional empathy, it is presently unclear whether psychopathic traits are differentially related to empathic concern versus affective sharing. This is a particularly important question given that “empathy” is used to refer to multiple phenomena, which may differentially relate to behavioural outcomes. For example, evidence suggests that empathic concern, but not personal distress, gives rise to altruistic motivation (Batson, Fultz, & Schoenrade, 1987). As well, these phenomena may vary independently in some disorders. For example, frontotemporal dementia, which features empathy deficits, has been associated with impaired affective sharing but intact empathic concern (Oliver et al., 2015).

In the general population, evidence suggests that psychopathic (Edens, Marcus, Lilienfeld, & Poythress, 2006; Hare & Neumann, 2008) and autistic (Constantino & Todd, 2003; Posserud, Lundervold, & Gillberg, 2006) traits are continuously distributed. However, little is known about how individual differences in these traits map onto facets of empathic performance. There is some evidence that affective-interpersonal psychopathic trait levels are negatively correlated with questionnaire measures of empathic concern and feelings of positivity or negativity in response to emotional faces and stories (Seara-Cardoso, Dolberg, Neumann, Roiser, & Viding, 2013; Seara-Cardoso, Neumann, Roiser, McCrory, & Viding, 2012). Other work has shown that autistic trait levels in neurotypical adults are inversely associated with performance on theory of mind tasks (Baron-Cohen, Wheelwright, Hill, et al., 2001; Miu, Pana, & Avram, 2012; Voracek & Dressler, 2006). Bridging these findings, Lockwood et al. (2013) observed

distinct relationships between high psychopathic traits and reduced valence ratings in response to emotional faces, and high autistic traits and diminished theory of mind performance in a community sample. However, this study did not include a measure of empathic concern. Thus, the relationship between psychopathic versus autistic traits with dissociable empathy indices has rarely been examined in healthy individuals.

Like psychopathic and autistic traits, trait anxiety varies continuously in the general population (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), and may have important implications for empathic responding. For example, arousal is widely considered to be a component of empathic responding (Decety, Norman, Berntson, & Cacioppo, 2012; Decety, Smith, Norman, & Halpern, 2014), and increased autonomic arousal to emotional stimuli has been observed in individuals with higher levels of emotional empathy (de Sousa et al., 2010; Mehrabian, Young, & Sato, 1988). Indeed, autonomic arousal is sometimes assumed to be an index of emotional empathy (Blair et al., 1997). Further, opposing patterns of amygdala activation have been associated with trait anxiety (Stein, Simmons, Feinstein, & Paulus, 2007) and emotional empathy (Seara-Cardoso, Sebastian, Viding, & Roiser, 2015) levels, suggesting that there may be overlap in the neurocognitive substrates driving these phenomena. However, despite the theoretical influence of trait anxiety on empathy, the inclusion of both anxiety and empathy indices is rare, and little work has focused on elucidating their association.

The present study had two main objectives. The first was to determine whether coldhearted psychopathic and autistic traits in a community sample are differentially associated with cognitive empathy, empathic concern, and affective sharing performance. Coldhearted psychopathic traits reflect the core emotional features of psychopathy, including a void of empathy and callousness towards others (Lilienfeld & Widows, 2005). Coldheartedness is also correlated with other emotional empathy indices (Fecteau, Pascual-Leone, & Théoret, 2008; Sandoval, Hancock, Poythress, Edens, & Lilienfeld, 2000), and Factor 1 of the Hare Psychopathy Checklist – Revised (Poythress, Edens, & Lilienfeld, 1998). Thus, based on the existing literature, coldheartedness was expected to be inversely associated with emotional empathy ratings, including measures of both empathic concern and affective sharing, but not cognitive empathy accuracy. Conversely, we hypothesized that autistic trait levels would be negatively correlated with cognitive empathy accuracy, but not emotional empathy ratings. The

second key objective of this study was to elucidate the relationship between trait anxiety and empathy. Unlike coldhearted psychopathic traits, we hypothesized that anxiety would have a positive association with emotional empathy, but that the relationship would be less generalized. Specifically, we predicted that trait anxiety levels would be positively associated with measures of affective sharing, and arousal ratings in particular. This marks the first time that performance-based measures of cognitive empathy, empathic concern, and affective sharing have been indexed in relation to individual differences in psychopathic, autistic, and anxious traits in the same community sample.

3.2 Methods

3.2.1 Participants

Ninety healthy individuals (54 females, 36 males) with a mean age of 21.7 years (range 18-36, $SD = 3.2$) took part in the experiment. As determined by screening, all participants were in good physical health and had no history of neurological disease, psychiatric problems, or head injury. Participants also had normal or corrected-to-normal vision and none reported colour blindness. Flyers were used for participant recruitment. All participants granted informed consent and were compensated \$30 for their participation. This study was approved by the Health Sciences Research Ethics Board at the institution of research.

The present study was conducted alongside another distinct experiment. The order of task completion was randomized across participants. All participants completed the pertinent measures for this investigation.

3.2.2 Measures

3.2.2.1 Multifaceted Empathy Test (MET; Dziobek et al., 2008; Figure 3.1)

The MET is a performance-based multi-dimensional measure of empathy. During the MET, participants answer questions which dissociably tap cognitive and emotional empathy in response to naturalistic emotionally-charged images. Each question was presented on a screen that also displayed the relevant image, and slide presentation was controlled by the researcher. All ratings were provided using a 9-point Likert scale with pictograms from the Self-Assessment Manikin (Lang, Bradley, & Cuthbert, 1997). Responses were voiced aloud and recorded by the researcher. Task completion required approximately 30 minutes. The MET consists of 23 pairs of realistic positive and negative images: a context-only picture, and a social picture with emotional individuals in this context. For each context-only picture, participants are asked to provide a valence rating and an arousal rating. For the social stimuli, cognitive empathy is indexed by asking participants how the person or people in the picture are feeling from four possible choices. Participants then provide an intensity rating for the emotional experience of the person or people in the picture. Two aspects of emotional empathy are also evaluated, corresponding to empathic concern and affective sharing (also known as emotional mirroring). Empathic concern is measured by asking how happy participants are for people in positive images or their level of concern for people in negative images. Finally, affective sharing is indexed via an intensity rating to indicate the degree of shared emotional experience with people in the pictures, a valence rating, and an arousal rating. Table 3.1 includes a summary of the MET measures of interest. We opted not to include the cognitive empathy intensity measure in our data analysis because it may share features of both cognitive and emotional empathy.



Figure 3.1 The Multifaceted Empathy Test

Example taken from the Multifaceted Empathy Test (MET; Dziobek et al., 2008) of a context-only image with the valence rating and response scale (left), and the corresponding social image with the empathic concern rating and response scale (right).

Table 3.1: MET measures of interest

Measure	Question	Response
Cognitive Empathy	How do you think this person is feeling?	Choice from 4 possible mental states
Emotional Empathy		
Empathic Concern	How concerned are you for this person? (negative stimuli) How happy are you for this person? (positive stimuli)	1 = not at all, 9 = completely
Affective Sharing		
Intensity	When looking at this picture, does it make YOU feel _____ at all? If so, how _____ do you feel?	1 = not at all, 9 = completely
Valence	How positive or negative does this picture make you feel?	1 = most positive, 9 = most negative
Arousal	How calm or aroused does this picture make you feel?	1 = most calm, 9 = most aroused
Context-Only		
Valence	How positive or negative does this picture make you feel?	1 = most positive, 9 = most negative
Arousal	How calm or aroused does this picture make you feel?	1 = most calm, 9 = most aroused

3.2.2.2 *Psychopathic Personality Inventory - Revised (PPI-R; Lilienfeld & Widows, 2005)*

The PPI-R is a 154-item self-report questionnaire tapping global psychopathy and its component traits. It is comprised of eight subscales, including Coldheartedness, which encompasses the fundamental affective features of psychopathy, such as callousness and a lack of empathy, loyalty, and guilt. Responses are made on a 4-point scale ranging from “False” to “True”, including items such as “I look out for myself before I look out for anyone else”.

3.2.2.3 *Autism Spectrum Quotient (AQ; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001)*

The AQ assesses autistic traits in healthy adults. The AQ is a 50-item self-report measure evaluating social skills, attention to detail, attention switching, imagination, and communication. Questions, such as “I find it difficult to imagine what it would be like to be someone else”, are answered on a 4-point scale ranging from “Definitely Agree” to “Definitely Disagree”.

3.2.2.4 *State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983)*

The STAI is a self-report measure including 20 items assessing trait anxiety, which refers to anxiety as a general state and captures an enduring disposition, such as “I worry too much over something that really doesn’t matter”. Responses are made on a 4-point scale ranging from “Not At All” to “Very Much So”.

3.2.3 *Data analysis*

According to inspection of normal Q-Q plots and the Shapiro-Wilk Test, Coldheartedness T scores, $p < .001$, Trait Anxiety Inventory scores, $p < .01$, Cognitive Empathy accuracy, $p < .001$, and Empathic Concern ratings, $p < .01$, deviated significantly from normality. Accordingly, positively skewed distributions (Coldheartedness and trait anxiety) were log transformed and

negatively skewed distributions (Cognitive Empathy and Empathic Concern) were reverse-scored then log transformed. These transformed variables were utilized in subsequent analyses as they did not deviate significantly from normality, $p > .1$, with the exception of Cognitive Empathy accuracy, which remained positively skewed due to most participants performing at ceiling. PPI-R data from two participants were also excluded because their scores were within the 'highly atypical' range on both of the embedded Inconsistent Responding scales, indicating that their responses were inconsistent and invalid according to PPI-R guidelines (Lilienfeld & Widows, 2005).

Bivariate correlation analyses were first conducted to investigate the zero-order associations between measures of cognitive and emotional empathy on the MET, and coldheartedness, autistic trait, and trait anxiety levels.

In order to elucidate the relationship between the set of trait questionnaire measures and the set of behavioural empathy measures, a canonical correlation analysis was also conducted. Canonical correlation produces maximized correlations between a weighted sum (linear combination) of predictor variables and a weighted sum of criterion variables. It is designed to draw out latent relations between the two theoretically-related sets of variables [the topic and related analyses, notably as applied to personality research, are reviewed in Neufeld (1977) and Neufeld and Gardner (1990)]. Canonical correlation reduces the concatenated array of bivariate correlations to a set of canonical functions expressing the main sources of overlap between the measurement sets. Each canonical function is accompanied by a redundancy index, which indicates the average predictability of the individual measures in one set from an optimal combination of those in the other set.

The predictor variables included in the analysis were Coldheartedness, AQ, and trait anxiety scores, and the criterion variables included each of the MET measures. No multivariate outliers were apparent in the predictor variable set (Mahalanobis distance values less than the critical chi-square value of 16.27, $df = 3$, $p < .001$) or the criterion variable set (Mahalanobis distance values less than the critical chi-square value of 24.32, $df = 7$, $p < .001$).

Lastly, partial correlation analyses were implemented to examine the relationship between emotional empathy indices and levels of personality traits, while controlling for arousal generated by context, or non-social aspects of the images.

3.3 Results

3.3.1 Bivariate correlation analysis

The zero-order correlations among all the variables of interest are reported in Table 3.2. Importantly, a wide range of scores was found on the personality trait measures, including psychopathic trait scores (PPI-R total scores: $M = 58^{\text{th}}$ percentile, range 1st-99th percentile; Coldheartedness scores: $M = 53^{\text{rd}}$ percentile, range 3rd-99th percentile), autistic trait levels ($M = 16$, range 2-32, Max 50), and trait anxiety levels ($M = 37$, range 22-60, Max 80). Of particular interest, Coldheartedness was found to be moderately negatively correlated with Empathic Concern, somewhat less strongly with Affective Sharing Valence and Affective Sharing Intensity, and more weakly with Context-Only Valence ratings. Interestingly, Coldheartedness was not correlated with arousal ratings. No significant relationships were identified between autistic traits and any of the performance-based empathy measures, including Cognitive Empathy; although, autistic trait levels were positively associated with trait anxiety levels. Notably, there was no significant relationship between trait anxiety and Coldheartedness. However, trait anxiety was positively correlated with Affective Sharing Arousal and Context-Only Arousal. It was not significantly associated with Empathic Concern, but there was a marginal positive association with Affective Sharing Intensity, $p = .061$, and Context-Only Valence ratings, $p = .054$.

Steiger's Z-tests for dependent correlations were also performed to determine whether Coldheartedness was differentially associated with Empathic Concern versus Cognitive Empathy, and whether Coldheartedness and trait anxiety were differentially related to the measures of empathic concern and arousal towards social stimuli. These revealed that Coldheartedness was significantly more weakly correlated with Cognitive Empathy than with

Empathic Concern, $Z = -3.13$, $p < .01$. Additionally, Coldheartedness was significantly more strongly associated with Empathic Concern than trait anxiety was, $Z = -3.82$, $p < .001$. However, the correlations between Coldheartedness versus trait anxiety and Affective Sharing Arousal were not found to be significantly different, $Z = -1.61$, $p = .1$.

Table 3.2: Bivariate correlations between variables of interest

	1	2	3	4	5	6	7	8	9	10
1 Coldheartedness	--	-.044	-.115	-.060	-.498***	-.322**	-.370***	.022	-.216*	.081
2 Autism Spectrum Quotient		--	.491**	.077	-.092	-.057	.102	.083	.061	.124
3 Trait Anxiety Inventory			--	.098	.067	.198	.124	.275**	.204	.307**
4 MET Cognitive Empathy				--	-.010	-.046	-.003	-.060	-.031	-.089
5 MET Empathic Concern					--	.798***	.679***	.507***	.429***	.364***
6 MET Affective Sharing Intensity						--	.689***	.662***	.532***	.544***
7 MET Affective Sharing Valence							--	.455***	.771***	.369***
8 MET Affective Sharing Arousal								--	.380***	.873***
9 MET Context-Only Valence									--	.446***
10 MET Context-Only Arousal										--

* $p < .05$ ** $p < .01$ *** $p < .001$

3.3.2 Canonical correlation analysis

A canonical correlation analysis was also conducted in order to determine the relationship between the questionnaire trait measures as a weighted whole (predictor variables) and the MET behavioural empathy measures (criterion variables). Two significant canonical functions emerged between the sets of variables, $R_c = .627$, Wilk's $\lambda = .467$, $p < .001$, $R_c = .407$, Wilk's $\lambda = .769$, $p < .05$. See Table 3.3 for details. The main predictor loading onto the first canonical function was Coldheartedness (.947). The main criterion variables loading onto this canonical function were Empathic Concern (-.780), Affective Sharing Intensity (-.462), and Affective Sharing Valence (-.513). The redundancy indices for the predictor and criterion variables were .128 and .069, respectively. This canonical function demonstrates a link between high coldheartedness levels and lower levels of empathic concern, reduced shared feeling intensity, and diminished feelings of negativity or positivity in response to social images. Notably, greater Coldheartedness was specifically linked to ratings of the social stimuli, as opposed to the context-only images.

The main predictor loading onto the second canonical function was trait anxiety (.702). The main criterion variables loading onto this function were Affective Sharing Intensity (.632), Affective Sharing Arousal (.558), and Context-Only Arousal (.565). To a lesser degree, Empathic Concern (.349) and Context-Only Valence (.393) also loaded onto the second canonical function. The redundancy indices for the predictor and criterion variables were .032 and .031, respectively. This function illustrates a strong relationship between high trait anxiety and increased levels of arousal in response to both social and non-social stimuli, and greater shared feeling intensity.

Table 3.3: Canonical loadings for questionnaire trait measures and MET behavioural empathy measures

Variables	Canonical Loadings (N= 88)	
	Canonical Function	
Predictor Set	I	II
Coldheartedness	.947	-.061
Autism Spectrum Quotient	.244	-.280
Trait Anxiety Inventory	.155	.702
Criterion Set		
MET Cognitive Empathy	-.043	.111
MET Empathic Concern	-.780	.349
MET Affective Sharing Intensity	-.462	.632
MET Affective Sharing Valence	-.513	.065
MET Affective Sharing Arousal	.133	.558
MET Context-Only Valence	-.261	.393
MET Context-Only Arousal	.246	.565

3.3.3 Partial correlation analysis

Partial correlations were also computed to control for the effects of Context-Only Arousal on the associations between indices of emotional empathy and levels of personality traits of interest. Partial correlations among these variables of interest are reported in Table 3.4. The correlations between Coldheartedness and Empathic Concern, Affective Sharing Intensity, and

Affective Sharing Valence remained significant, and were more strongly negatively correlated, after controlling for Context-Only Arousal. Conversely, controlling for the effect of Context-Only Arousal rendered the correlation between trait anxiety levels and Affective Sharing Arousal non-significant, and the relationship between trait anxiety and Affective Sharing Intensity no longer marginally significant.

Table 3.4: Partial correlations controlling for MET Context-Only Arousal between variables of interest

	1	2	3	4	5	6	7
1 Coldheartedness	--	-.055	-.147	-.568***	-.435***	-.428***	-.098
2 Autism Spectrum Quotient		--	.475***	-.136	-.138	.064	-.050
3 Trait Anxiety Inventory			--	-.029	.056	.006	.016
4 MET Empathic Concern				--	.762***	.636***	.418***
5 MET Affective Sharing Intensity					--	.625***	.458***
6 MET Affective Sharing Valence						--	.289**
7 MET Affective Sharing Arousal							--

* p < .05 ** p < .01 *** p < .001

3.4 Discussion

Past investigations of clinical populations have revealed an association between psychopathy and deficient emotional empathy, as well as between autism spectrum disorder and impaired cognitive empathy or theory of mind. However, little is known regarding the relationship between behavioural measures of cognitive empathy, empathic concern, and affective sharing, and individual differences in psychopathic, autistic, and anxious traits. Distinguishing the relationship at a more refined level is of particular interest given that the term “empathy” refers to heterogeneous phenomena with different implications for social behaviour. The present study helped address this gap in knowledge using behavioural indices of cognitive empathy and several components of emotional empathy. In line with expectations, coldhearted psychopathic traits were found to be negatively correlated with elicited emotional empathy, including empathic concern and affective sharing, and unrelated to cognitive empathy accuracy. As predicted, autistic traits were not associated with the levels of empathic concern or affective sharing experienced; however, they were also unrelated to cognitive empathy performance. In addition, though trait anxiety levels were positively linked to certain aspects of emotional

empathy, and arousal in particular, this appeared to be driven by arousal in response to contextual elements as opposed to social aspects of the stimuli. Furthermore, there was little evidence that trait anxiety was related to empathic concern. In contrast, the social content of the images seemed to underlie the inverse relationship between coldheartedness and emotional empathy.

3.4.1 Coldhearted psychopathic traits and empathy

Evidence for an emotional empathy impairment in psychopathy is predominantly inferred from potentially ambiguous outcome measures, including recognition deficits (Hastings et al., 2008), abnormal activation in emotion-related neural regions (Decety, Skelly, et al., 2014), and diminished autonomic arousal (Blair et al., 1997) in response to affective stimuli. Questionnaires and some performance-based measures of emotional empathy have also been utilized. For example, in healthy adults, affective psychopathic traits have been negatively associated with questionnaire measures of empathic concern or affective empathy more generally (Mahmut, Homewood, & Stevenson, 2008), and ratings on valence-based affective resonance tasks (Lockwood et al., 2013; Seara-Cardoso et al., 2013; Seara-Cardoso et al., 2012). However, there is a need for more explicit demonstrations of impaired empathic responding, and a clear delineation of the aspects of empathy that are affected in individuals with psychopathic tendencies. Recently, Lishner et al. (2012) developed a task that covertly assesses empathic concern and affective sharing induced by images of basic emotional expressions and an emotional story. To date, however, the results using this task have been mixed. One investigation did not provide strong evidence for a link between psychopathic trait levels and empathic concern or affective sharing in either community or forensic samples (Lishner et al., 2012). Notably, the authors identified the relatively low levels of psychopathic traits in these groups in comparison to normative samples as a potential caveat. A more recent study reported a negative relationship between callous affect and both empathic concern and affective sharing in healthy adults (Lishner, Hong, Jiang, Vitacco, & Neumann, 2015).

The current work expands what is known about the relationship between callous psychopathic traits and emotional empathy. Presently, we provide clear evidence of an inverse

relationship between coldheartedness and the elicitation of empathic concern and affective sharing in healthy adults with a wide range of psychopathic trait scores. Among other important outcomes, this suggests that increased coldheartedness may be linked to reduced prosocial behaviour, as empathic concern has been found to result in altruistic motivation (Batson, Duncan, Ackerman, Buckley, & Birch, 1981; Edele, Dziobek, & Keller, 2013). We also extend previous behavioural findings by examining the link between affective psychopathic traits and different aspects of affective sharing. In particular, we have demonstrated a negative association between coldheartedness and the degree to which participants shared the feelings of people in emotional images (Affective Sharing Intensity). Coldheartedness was also inversely related to how positive or negative the social images made participants feel (Affective Sharing Valence), but unrelated to arousal levels (Affective Sharing Arousal).

3.4.2 Autistic traits and empathy

In contrast to the demonstrated relationship with coldheartedness, and as predicted, no significant relationships were apparent between measures of emotional empathy and autistic trait levels. It should be noted that some investigations have found an emotional empathy deficit according to self-report measures in individuals with autism spectrum disorder (Mathersul et al., 2013b, 2013d; Shamay-Tsoory et al., 2002), though our results support no link between autistic traits as they vary in a community sample and reduced emotional empathy. Autistic traits were unexpectedly also found to be unrelated to cognitive empathy performance. This finding is likely attributable to a ceiling effect, given that the mean Cognitive Empathy accuracy in this sample was 94%, $SD = 0.046$. Prior investigations have demonstrated a negative association between autistic traits and cognitive empathy performance in community samples (Baron-Cohen, Wheelwright, Hill, et al., 2001; Miu et al., 2012; Voracek & Dressler, 2006). Though the MET has been utilized to demonstrate a deficit in cognitive but not emotional empathy in adults with autism spectrum disorder (Dziobek et al., 2008), this version may not be sensitive enough to detect individual differences in cognitive empathy ability in healthy populations. Further, Cronbach's alpha for the cognitive empathy scale in this version of the MET was 0.71 (Dziobek et al., 2008), which may make it more difficult to identify relationships with performance on this

scale. Despite this, our data regarding autistic traits and emotional empathy remain informative. We had a range of autistic trait levels in our sample, and in accordance with demonstrations of heightened anxiety in clinical autistic populations (White, Oswald, Ollendick, & Scahill, 2009), they were found to be positively associated with trait anxiety levels.

3.4.3 Trait anxiety and empathy

In addition to indices of coldhearted and autistic traits, this investigation is unique in its examination of trait anxiety in relation to empathic responding. This is of particular interest because trait anxiety is implicated in arousal and may be linked to empathy on both a conceptual and neurocognitive level. For example, high trait anxiety is associated with an increased risk for mood and anxiety disorders, and both trait anxiety (Stein et al., 2007) and mood disorders (Beesdo et al., 2009; Davis, 1992) have been associated with amygdala hyperactivity. In contrast, high callous psychopathic traits (Blair, 2013a; Marsh et al., 2013) and diminished emotional empathy are associated with reduced amygdala responsiveness (Seara-Cardoso et al., 2015). Thus, neurocognitive systems that are thought to drive empathy overlap with those implicated in negative affect, including anxiety. Accordingly, we found that heightened trait anxiety was associated with increased affective sharing intensity and heightened arousal ratings in response to social stimuli. However, higher trait anxiety was also strongly linked to greater arousal ratings in response to context-only stimuli. Interestingly, controlling for context-only arousal ratings revealed that these accounted for the apparent relationship between the levels of affective sharing elicited by the stimuli and trait anxiety levels. In contrast, context-only arousal did not account for the associations between aspects of emotional empathy and coldheartedness. This suggests that whereas coldheartedness may be particularly linked to emotional responding to social images, trait anxiety is likely related to a more generalized arousal response that is less clearly associated with the social aspects of stimuli. Further, the level of empathic concern experienced was more strongly correlated with coldheartedness than trait anxiety. These findings have significant implications for models of empathy. Specifically, though the neurocognitive systems associated with trait anxiety (Stein et al., 2007) and empathy (Seara-Cardoso et al., 2015) may have some overlap, our results suggest that they are not identical. As well, there is evidence that

empathic concern motivates altruistic behaviour and the desire to relieve the stress of another individual in need (Batson et al., 1981; Pavey, Greitemeyer, & Sparks, 2012). In contrast, personal distress pertains to self-oriented feelings of anxiety and discomfort, and has been associated with motivation to relieve one's own discomfort and stress as opposed to motivating proactive behaviours that relieve another's distress (Batson, 1991). It is therefore possible that decreased coldheartedness levels are more closely linked with prosocial behavioural outcomes in response to the affective experience of another individual. In contrast, high trait anxiety may have fewer implications for motivating altruistic behaviours.

3.4.4 Limitations and future directions

Although the MET allows for the assessment of empathy elicited online, responses are subjective and therefore susceptible to response bias, such as socially desirable responding. The addition of physiological measures could be beneficial for the validation of subjective arousal ratings. Though patients with autism spectrum disorder (Gu et al., 2015; Mathersul et al., 2013b) and psychopathy (Blair, 2005; Blair et al., 1997) exhibit impaired empathy and often atypical autonomic arousal, rarely do investigations include behavioural indices of empathy in conjunction with physiological measures. Future studies including both types of measures would be helpful for delineating the relationship between arousal and empathic experience.

Also, the MET Empathic Concern questions are phrased in such a way that it precludes participants from expressing sadistic or otherwise contrary responses (happiness for people in negative images and concern for those in positive images). This procedure may therefore bias responding. However, we would expect that rates of sadistic responding would be very low in our population. Indeed, recent work suggests that even in prison populations sadism is only very modestly correlated with psychopathy, and the two phenomena should be considered distinct constructs (Robertson & Knight, 2014).

A few issues concerning measurement should be noted, as well. For example, the potential ceiling effect and restricted range of cognitive empathy performance limited interpretations related to this measure. There is also no gold standard for measuring psychopathy

in a community sample. We focused on the Coldheartedness subscale of the PPI-R due to its association with the fundamental interpersonal and affective aspects of psychopathy (Poythress et al., 1998). Increased coldheartedness in the healthy population has also been linked to functional abnormalities in emotion-relevant neural regions in response to affective stimuli (Han, Alders, Greening, Neufeld, & Mitchell, 2011; Harenski, Kim, & Hamann, 2009), aberrant interpersonal behaviour (Vieira & Marsh, 2014), and reduced awareness of peri-threshold fearful expressions (Oliver, Mao, & Mitchell, 2014). However, being that the construct of psychopathy includes a constellation of factors, it is important to note that the conclusions drawn relate specifically to coldhearted psychopathic traits rather than psychopathy overall. In addition, the inclusion of a depression index would have been useful in determining whether depressive symptoms influenced empathic responding and the relationship between anxiety and empathy, given that depression is highly comorbid with anxiety (Brown, Campbell, Lehman, Grisham, & Mancill, 2001) and has been associated with empathy deficits (Schreiter, Pijnenborg, & aan het Rot, 2013).

Lastly, canonical correlation analysis assesses predictor variables in tandem, such that delineating their individual effects can be challenging. Presently, the very high respective loadings of Coldheartedness and trait anxiety on the two significant canonical functions allowed us to draw conclusions about these particular predictor variables in relation to the criterion variables. It is important to note that it is the specific combination of the predictor variables that is associated with the particular combination of criterion variables for each canonical function. Nevertheless, our interpretation of the results is supported by considering the canonical functions in combination with the bivariate and partial correlations.

3.5 Conclusions

The present investigation provides significant insight into how individual differences in coldhearted psychopathic traits, autistic traits, and trait anxiety are associated with cognitive empathy, empathic concern, and affective sharing in a community sample. Crucially, increased coldheartedness was associated with reduced empathic concern and dampened vicarious emotional experience across a variety of complex and more basic positive and negative

emotional states, a pattern of responding that has been associated with reductions in prosocial behaviour. In addition, as predicted, autistic traits were found to be unrelated to emotional empathy. A link between heightened trait anxiety and increased affective sharing was also identified, but this appeared to be driven by arousal elicited by contextual as opposed to social elements of the stimuli. Accordingly, trait anxiety may influence subjective affective experience via generalized arousal, but the emotional aspects affected do not appear to be important for motivating one to care for another or for increasing shared emotional experience. Due to the difficulties associated with extrapolating findings from community to clinical populations (e.g., Blair, 2013b), conclusions regarding clinically significant levels of psychopathy, autism, and anxiety should be made with caution. Nevertheless, the current findings raise the possibility that there could be a disconnect between arousal generated in response to an emotional scene and empathic concern. Therefore, any physiological response generated to such scenes should not be considered evidence that an individual or group will necessarily exhibit prosocial behaviours in response to such situations. Furthermore, the generation of arousal to emotional situations may not in itself be a sufficient index of treatment success for disorders featuring abnormalities in empathy. Future work in clinical populations including behavioural measures of both empathic concern and affective sharing would be beneficial to gain further insight into empathic experience and potential treatment targets for these patients.

3.6 References

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Chapter 4

4 The Neurocognitive Correlates of Distinct Facets of Empathy: Greater Involvement of Simulation Mechanisms in Emotional Relative to Cognitive Empathy

Abstract

Empathy is a crucial component of successful interpersonal interactions, and it is impaired in many debilitating disorders. Empathy is largely considered to be a multidimensional construct, including cognitive empathy (the ability to adopt another's perspective) and emotional empathy (the capacity to share and react affectively to another's emotional experience). It has been suggested that action-perception matching, or simulation mechanisms, may facilitate empathy by supporting the simulation of perceived experience in others. However, whether simulation mechanisms are involved in the experience of cognitive or emotional empathy remains unclear, and no studies to date have quantitatively compared the involvement of the simulation network in cognitive versus emotional empathy. Presently, healthy adults underwent functional magnetic resonance imaging while completing a false belief task targeting cognitive empathy and an emotional empathy task assessing how strongly they felt for people in emotional images. Simulation regions were also localized using a button-pressing task. Conjunction analyses revealed common recruitment of the inferior frontal gyrus (IFG), a region thought to be critical for action-perception matching, during both simulation and emotional, but not cognitive, empathy. Critically, greater activation was also observed in identified simulation regions in the left IFG during emotional as compared to cognitive empathy. Further, a positive correlation was demonstrated between activity during emotional empathy in a simulation area in the left IFG and mean feeling ratings expressed during the emotional empathy task. These findings provide strong evidence for greater involvement of simulation mechanisms in emotional empathy than cognitive empathy. Thus, the simulation network may be of particular interest in disorders featuring emotional empathy impairments.

4.1 Introduction

Empathy is a crucial component of interpersonal interactions thought to influence prosocial behaviour, and it is impaired in many debilitating disorders, such as frontotemporal dementia (Dermody et al., 2016; Oliver et al., 2015), schizophrenia (Green, Horan, & Lee, 2015), borderline personality disorder (Dziobek et al., 2011), psychopathy (Blair, 2005), and autism spectrum disorder (Baron-Cohen, Leslie, & Frith, 1985; Mathersul, McDonald, & Rushby, 2013). It has been suggested that empathy may be facilitated through the embodied simulation or internal representation of perceived experience in others (Bastiaansen, Thioux, & Keysers, 2009; Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Gallese, 2001; Gallese, Keysers, & Rizzolatti, 2004; Iacoboni, 2009; Pineda, Moore, Elfenbein, & Cox, 2009; Preston & de Waal, 2002). This simulation is thought to be achieved via an action-perception neural matching mechanism. For example, interpersonal understanding or shared emotional experience may emerge while watching someone dance to their favourite song due to activation of some of the same neural regions as when you are dancing yourself. The discovery of mirror neurons in the ventral premotor cortex (PMC) into inferior frontal gyrus (IFG), and inferior parietal lobule (IPL) of macaque monkeys, which fire during both observation and execution of goal-related actions, provided a potential neural basis for this simulation mechanism (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Fogassi et al., 2005; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996). In humans, although the existence and role of mirror neurons is disputed (Caramazza, Anzellotti, Strnad, & Lingnau, 2014; Turella, Pierno, Tubaldi, & Castiello, 2009), functional imaging studies of action observation, execution, and imitation suggest that such a system is subserved by analogous circuitry including the ventral PMC into posterior IFG and the IPL (Caspers, Zilles, Laird, & Eickhoff, 2010; Molenberghs, Cunnington, & Mattingley, 2012). Thus, the IFG and IPL are engaged during both action observation and execution, and are thought to be critical areas for this observation-execution matching simulation mechanism (Gallese, 2001; Rizzolatti & Craighero, 2004). The posterior superior temporal sulcus (STS) does not appear to contain observation-execution matching neurons as it does not respond during action execution in isolation, but is activated during action observation and imitation, and thought to be the primary visual input to these critical simulation areas via the IPL (Iacoboni et al., 2001; Keysers & Perrett, 2004). Within this network, it is believed that the posterior STS provides a visual description of actions, the IPL codes motor aspects of actions, and the goal of

the action is coded by the ventral PMC/IFG (Iacoboni, 2005; Iacoboni & Dapretto, 2006; Keysers & Perrett, 2004). Presently, we refer to this circuitry, also known as the mirror neuron system, as the 'simulation network'. Of particular interest, even the observation and imitation of emotional expressions in humans elicits increased activity in areas of the simulation network (Carr et al., 2003; Leslie, Johnson-Frey, & Grafton, 2004; Montgomery & Haxby, 2008). Thus, it has been proposed that these frontal and parietal simulation regions generate a motor representation of other individuals' mental or emotional states.

Whether a simulation mechanism may facilitate empathy is complicated by evidence that empathy is a multidimensional construct, including both cognitive and emotional facets (Eslinger, 1998; Shamay-Tsoory, 2011). Cognitive empathy refers to the capacity to adopt another individual's perspective, and thereby infer their mental or emotional state, and is often used interchangeably with theory of mind (Blair, 2005; Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004). Emotional empathy involves the ability to share and react affectively to the emotional experience of another individual. The dissociability of these facets is supported by behavioural data from different clinical populations (Lockwood, Bird, Bridge, & Viding, 2013) and lesion data (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). Functional imaging studies have also provided evidence for this, with meta-analyses demonstrating that cognitive empathy typically elicits activity in areas including the medial prefrontal cortex (mPFC), temporoparietal junction (TPJ), STS, and precuneus (Bzdok et al., 2012; Carrington & Bailey, 2009; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014; Van Overwalle, 2009). Alternatively, emotional empathy has been associated with activation in areas including the anterior insula, anterior cingulate cortex, IFG, and sometimes the amygdala (Bzdok et al., 2012; Fan, Duncan, de Greck, & Northoff, 2011; Lamm, Decety, & Singer, 2011; Shamay-Tsoory, 2011; Walter, 2012). Although there is some evidence that the simulation network may be involved in the experience of both cognitive and emotional empathy, this remains uncertain.

With respect to cognitive empathy, it has been proposed that the simulation network may influence this by way of the posterior STS/TPJ, providing rapid goal-related information from others' actions (Tramacere & Ferrari, 2016; Van Overwalle, 2009). The simulation network has been implicated in several aspects of cognitive empathy, including intention understanding and mental state attribution. Specifically, support for the involvement of the simulation network in

cognitive empathy initially came from findings of increased IFG activation to actions when they were embedded in contexts congruent with the intention of the action (e.g., grasping a cup to drink in the context of a breakfast ready to be eaten versus grasping it to clean up; Iacoboni et al., 2005; Kaplan & Iacoboni, 2006). Activity in the IFG and IPL has also been observed during mental state attribution for facial and bodily expressions (Lawrence et al., 2006). Further, mental state attribution accuracy has been found to modulate activation in simulation regions (Zaki, Weber, Bolger, & Ochsner, 2009), as well as being positively associated with mu suppression, a reputed electroencephalography (EEG) marker of simulation network activity (Pineda & Hecht, 2009). However, another functional magnetic resonance imaging (fMRI) study found that the degree of mental state content in participants' descriptions of others' actions did not modulate activity in simulation areas (Spunt, Satpute, & Lieberman, 2011). Additionally, a negative association has been identified between questionnaire scores of perspective taking, an aspect of cognitive empathy, and mu suppression during the observation of hand movements (Milston, Vanman, & Cunnington, 2013). Lastly, and of particular relevance, a conjunction analysis has demonstrated common activation in the posterior STS, but not in critical simulation areas including the IFG or IPL, between a cognitive empathy animation task and an action observation task used to define the simulation network (Ohnishi et al., 2004). Indeed, meta-analytic results have demonstrated that many fMRI investigations of cognitive empathy fail to find significant activation in putative critical simulation areas (Van Overwalle & Baetens, 2009). Thus, there is some support for a role of the simulation network in cognitive empathy, but results are limited and inconsistent.

Notably, it has also been suggested that the simulation network may underlie emotional empathic experience, influencing areas of the limbic system, such as the amygdala, via the IFG and the insula (Carr et al., 2003). Indeed, studies that have examined the involvement of the simulation network in both cognitive and emotional empathy have provided some support for greater involvement in emotional empathy. Specifically, questionnaire scores of emotional, but not cognitive, empathy have been positively correlated with IFG activation during the observation and imitation of emotional expressions (Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008) and gray matter volume of the right IFG and IPL (Cheng et al., 2009). Further, white matter integrity in the superior longitudinal fasciculus connecting temporoparietal regions to inferior frontal areas has also been positively associated with scores on questionnaire measures

of emotional, but not cognitive, empathy (Parkinson & Wheatley, 2014). Of particular note, one fMRI investigation found that emotional empathy recruited the right anterior PMC (BA 6) more than cognitive empathy, which was interpreted as evidence for greater engagement of the simulation network (Nummenmaa, Hirvonen, Parkkola, & Hietanen, 2008). However, this cluster was not identified using a simulation network localizer or compared to areas functionally defined as having simulation properties in other work. Thus, despite some evidence for greater involvement of the simulation network in emotional empathy, there is a lack of empirical evidence directly relating online emotional empathic responding to activation in these regions (Baird, Scheffer, & Wilson, 2011; Decety, 2010; Lamm & Majdandzic, 2015).

Taken together, though there is some support for a role of the simulation network in cognitive empathy, evidence suggests that it is more involved in emotional empathy. However, the degree to which simulation is implicated in these different facets of empathy remains unclear. Critically, no studies to date have statistically compared the involvement of the simulation network in cognitive versus emotional empathy. It is also important to note that prior investigations have largely provided evidence in the form of activation during empathy tasks in vast regions previously implicated in simulation, rather than areas functionally defined using a simulation network localizer. This is problematic because neurons that respond to both action observation and execution are believed to be found in specific areas of these larger implicated regions, and account for only a small proportion of the neurons in these areas in macaques (Decety, 2010). Correlations have also been demonstrated between questionnaire measures of empathy and activity in identified simulation regions, but these do not provide insight into the relationship between neural activity and the online experience of empathy. Accordingly, the objective of this study was to delineate the involvement of the simulation network in cognitive and emotional empathy. Crucially, this marks the first time that functional localizers will be used to determine the correspondence between brain areas identified as having simulation properties, and those recruited during cognitive and emotional empathy within the same participant population. This allows for a direct comparison of the extent to which cognitive and emotional empathy tasks modulate activity in functionally defined regions of the simulation network. Further, cognitive and emotional empathic abilities will be assessed during fMRI using behavioral indices, uniquely allowing for the determination of relationships between activation in localized simulation network regions and empathic responding. Our central hypothesis is that

regions within the simulation network critical for action-perception matching will be preferentially involved in the facilitation of emotional versus cognitive empathy. Specifically, regions of the localized simulation network identified using a button-pressing imitation task are expected to show some overlap with regions significantly activated during both the cognitive and emotional empathy tasks. However, critical simulation regions, including the ventral PMC into IFG and the IPL, are expected to be significantly more active during emotional as compared to cognitive empathy. Beyond evidence from prior work, the notion that shared neural representations should underlie the sharing of emotional experience involved in emotional empathy is logically consistent, especially given that emotional contagion, an automatic tendency to mimic expressions and postures of other individuals (Hatfield, Cacioppo, & Rapson, 1994), is thought to be a building block of emotional empathy (Decety & Meyer, 2008; Shamay-Tsoory, 2011). Lastly, behavioural indices of emotional empathy are expected to correlate more strongly with activity in the simulation network than behavioural measures of cognitive empathy.

4.2 Methods

4.2.1 Participants

Thirty-six healthy, right-handed individuals (19 females, 17 males) with a mean age of 21.5 years (range 18-26, $SD = 2.2$) took part in the experiment. As determined by screening, all participants were in good health and had no history of psychiatric problems, neurological disease, or head injury. Participants also had normal or corrected-to-normal vision and none reported colour blindness. All participants granted informed consent and were compensated for their participation. Flyers posted throughout campus at the University of Western Ontario were used for participant recruitment. This study was approved by the Health Sciences Research Ethics Board at the University of Western Ontario, London, Ontario, Canada.

4.2.2 Functional magnetic resonance imaging (fMRI) tasks

Participants underwent fMRI while performing four randomly presented tasks. Three of these tasks were utilized for the present investigation, including tasks tapping cognitive empathy, emotional empathy, and simulation. The fourth task involved viewing images of emotional individuals or hands performing an action, and providing a ‘yes’ or ‘no’ response as to how or why an individual was doing this. Prior to scanning, participants were presented with a practice version of the tasks which included one block of each condition type for each task with the same presentation times as the fMRI tasks. All tasks were programmed using E-Prime software (Schneider, Eschman, & Zuccolotto, 2002).

4.2.2.1 Cognitive empathy (Figure 4.1a)

The publicly available False Belief Task (Dodell-Feder, Koster-Hale, Bedny, & Saxe, 2011; Dufour et al., 2013) was used to localize brain regions recruited for cognitive empathy. Participants were presented with two types of visually presented short stories. False belief short stories described an individual’s false belief and their resultant actions, requiring belief inference, and false photo short stories described outdated, or no longer true, maps or pictures. False photo stories are utilized for the control condition because they are matched with the false belief stories for causal structure and difficulty, and also require the representation of false content (Saxe & Kanwisher, 2003). For each trial, stories were presented visually for 10 s, after which participants were asked to respond ‘true’ or ‘false’ via button press to a statement related to the false representation or reality of the situation. Placement of the ‘True’ and ‘False’ response options on either side of the screen was randomized on each trial to prevent a response bias from forming. Stimuli were presented on a black background in white font. The task included 24 stories per condition, presented in 3 runs of 4 blocks per condition (2 trials per block). Each block was followed by an inter-block interval of 18 s, during which a fixation cross was shown. The runs were presented in random order, and each one included a subset of stories that were randomly presented within the blocks. Accuracy for the cognitive empathy task was calculated as the proportion correct of the true or false questions following the false belief and false photo stories for each participant. Mean reaction times (RTs) were also determined for questions across

each condition. Paired t-tests demonstrated no significant difference in accuracy or RTs between false belief and false photo story questions, confirming the conditions were matched in difficulty (both $p > .1$; false belief accuracy: $M = 82.9\%$, $SD = 14\%$, range 42-100%; false photo accuracy: $M = 83.4\%$, $SD = 11\%$ range 54-100%; false belief RT: $M = 3120.36$, $SD = 360.2$, range 2472.67-3936.54; false photo RT: $M = 3074.33$, $SD = 347.0$ range 2512.58-3809.25).

4.2.2.2 Emotional Empathy (Figure 4.1b)

The emotional empathy task was based on the Multifaceted Empathy Test (Dziobek et al., 2011). The modified task includes only emotional empathy and control conditions. For feeling trials (emotional empathy), participants were presented with emotionally-charged naturalistic social images with a tagline conveying how people in the image are feeling, and asked how strongly they are feeling for people in the image. The emotional state of the individuals in the images was explicitly given to minimize the need for mental state inference (cognitive empathy) during the task. Responses were made on a four-point Likert scale from ‘not at all’ to ‘very strongly’ using a button box. The control condition consisted of age estimation trials; participants were presented with the same images without a tagline, and asked, “How old is this person?” Responses were made via button press on a four-point Likert scale from ‘very young’ to ‘very old’. Thus, the same images were presented in each condition, and similar response scales were utilized for both. Stimuli included 36 images (18 positive, 18 negative), taken from the Multifaceted Empathy Test (Dziobek et al., 2008) and supplemented with additional images from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2008). All images depict people in context varying in emotional expression, age, ethnicity, and gender. Images were presented for 8 s along with the relevant question and response scale. The task included the same 36 images per condition, presented in 3 runs of 4 blocks per condition (3 trials per block). Each block began with a 4 s instruction slide indicating which condition would follow by displaying the relevant response scale, and each one was followed by an inter-block interval of 18 s featuring a fixation cross. Run presentation was randomized, and each one contained a subset of images, balanced for valence, that were randomly presented within the blocks. For the emotional empathy task, mean feeling ratings were determined across all feeling

trials for each participant ($M = 3.06$, $SD = 0.51$, range 1.94-3.97). Mean RTs were also computed across each condition. Paired t-tests demonstrated that reaction times were significantly greater for feeling in comparison to age estimation responses ($p < .001$; feeling RT: $M = 2966.81$, $SD = 528.28$, range 1805.45-3826.81; age estimation RT: $M = 2143.80$, $SD = 369.06$, range 1517.33-2916.11).

4.2.2.3 Simulation (Figure 4.1c)

The simulation network localizer task was designed based on the paradigm used by Iacoboni et al. (1999) in order to identify brain regions activated during action imitation within the sample of individuals completing the cognitive and emotional empathy tasks. Participants were presented with images and video clips of an actor's hand pressing a button on a response box and asked to merely observe or execute a button press in response. Task stimuli were developed by the laboratory as part of a larger stimulus set depicting dynamic actions and expressions. To construct the stimulus set, amateur actors were recruited through a local theatre group and were compensated for their participation. Videos of actors' hands making a button press, as well as actors making particular facial expressions (for use in another investigation), were filmed and trimmed to a duration of 2 s. Videos from 24 actors (12 females and 12 males) used in the task feature left hands with either the index or middle finger being moved up and down to press a button on the same button box used by participants in the scanner. Still-frames were also taken from these videos (1 image per finger from each actor), and each one included a symbolic cue ('X') atop the index or middle finger to indicate the pressing finger. Simulation regions were identified using a contrast of action imitation versus action execution in response to a symbolic cue, as in previous investigations (e.g., Cross, Torrisi, Losin, & Iacoboni, 2013; Iacoboni et al., 1999; Koski, Iacoboni, Dubeau, Woods, & Mazziotta, 2003), on the basis that simulation areas are maximally activated during imitation (Iacoboni, 2009). Task conditions included observe-image ('Just watch the image'), execute-image ('Raise and lower the finger labeled X to press the button'), observe-video ('Just watch the video'), and imitate-video ('Imitate the finger movement in the video to press the button'). Still-frame images were presented during the -image conditions, whereas videos were presented during the -video

conditions. During the task, stimuli were presented for 2.5 s, followed by a fixation cross for 0.5 s. The task included the same 48 images and 48 videos (24 index finger, 24 middle finger each) for both of the image and video conditions, presented in 3 runs of 2 blocks per condition (8 trials per block). Each block began with a 4 s instruction screen indicating which condition would follow and a short description (shown above), and each one was followed by an inter-block interval of 18 s, during which a fixation cross was displayed. The runs were presented in random order, and each one included a subset of stimuli that were randomly presented within the blocks.

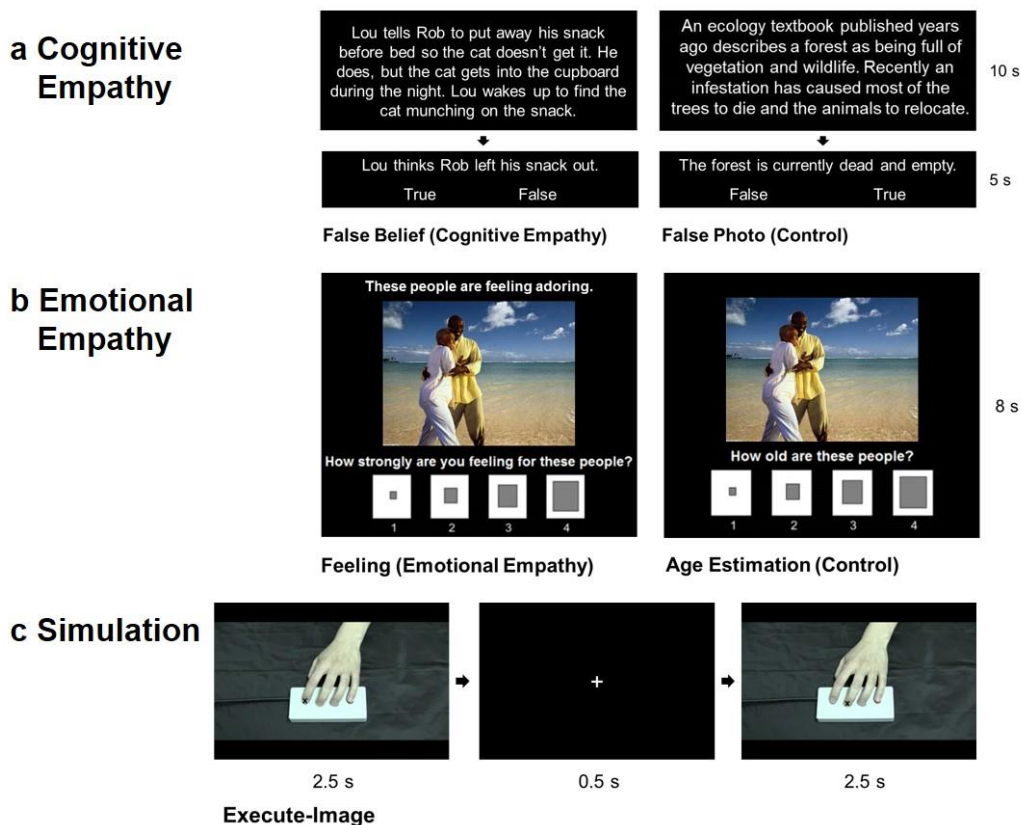


Figure 4.1 Trial examples for each of the fMRI tasks

(a) Trial structure for the False Belief Task (Dodell-Feder, Koster-Hale, Bedny, & Saxe, 2011; Dufour et al., 2013), including examples of false belief and false photo conditions. (b) Trial structure for the emotional empathy task (adapted from Dziobek et al., 2011), including examples of feeling and age estimation conditions. (c) Trial structure for the simulation network

localizer task (based on Iacoboni et al., 1999), including an example of the execute-image condition.

4.2.3 MRI data acquisition

Participants were scanned in a single session using a 3T Siemens Prisma scanner with a 32-channel head coil at Robarts Research Institute at the University of Western Ontario. fMRI images were taken with a T2*-gradient echo-planar imaging sequence [repetition time (TR): 3000 ms; echo time (TE): 30 ms; field of view (FOV): 20 cm; 80 x 80 matrix]. These parameters were chosen to optimize the signal-to-noise ratio for the amygdala (Morawetz et al., 2008; Robinson, Windischberger, Rauscher, & Moser, 2004) while still achieving complete brain coverage. For all functional scans, 50 contiguous slices of 2.5 x 2.5 mm in-plane with a slice thickness of 2.5 mm (forming voxels of 2.5 x 2.5 x 2.5 mm) were obtained. At the midway point of the scanning session, after completion of the second task, a high-resolution, T1-weighted, anatomical scan was obtained with whole-brain coverage (TR: 2300 ms; TE: 2.98 ms; FOV: 25.6 cm; 256 x 240 matrix; 192 axial slices; 1 x 1 x 1 mm voxels).

4.2.4 fMRI analysis

Individual and group analyses of fMRI data were conducted using the Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). Prior to performing analyses, images were motion corrected by registering all volumes of a given task to a functional volume adjacent to the anatomical scan. Within task runs, volumes were also censored, along with the preceding volume, if the derivatives of the six generated motion parameters had a Euclidean norm greater than 2.0 mm (Siegel et al., 2014). All data were spatially smoothed using a 4 mm full width at half maximum isotropic Gaussian kernel. The time series data were normalized such that each time point within a voxel was represented as a percent change from the mean voxel intensity. A general linear model was defined for each task for each participant. For each task, regressors for each condition were created by convolving the blocked stimulus events with a gamma-variate

hemodynamic response function. The blood-oxygen-level dependent (BOLD) response was fitted to each regressor to conduct linear regression modeling for each task. To account for voxel-wise correlated drifting, a baseline plus linear drift and quadratic trend were modeled to the time series of each voxel, as well. This produced a beta coefficient and t-statistic for each voxel at each regressor. Regression coefficients represented the percentage signal change from the mean activity. Group analyses involved transforming each participant's data into the standard space of Talairach and Tournoux (1988).

In addition to the regressors created for the task conditions (i.e., false belief and false photo for the False Belief Task, feeling and age estimation for the emotional empathy task, and observe-image, execute-image, observe-video, and imitate-video for the simulation task), regressors were made to model in-block instructions, for the emotional empathy and simulation tasks. Regressors of no interest were also created to model error-laden blocks from the simulation task. Blocks of the simulation task were deemed unusable if the participant did not follow the block instructions on at least 5 out of 8 trials (e.g., pressing during an observe block, or vice-versa). In order for a participant's data to be included for a specific condition, at least 4 out of 6 blocks per condition had to be usable. On the basis of these exclusion criteria, data from 6 participants were excluded from the simulation network localizer analysis, along with an additional participant's data due to computer error. For the False Belief Task, data from one participant was excluded due to a failure to understand the task.

A series of t-tests were conducted in AFNI to investigate within-task effects. These compared the whole-brain BOLD response to false belief versus false photo stories for the False Belief Task, feeling versus age estimation questions for the emotional empathy task, and imitate-video versus execute-image conditions for the simulation network localizer task. As in previous investigations (e.g., Cross et al., 2013; Iacoboni et al., 1999; Koski et al., 2003), simulation regions were identified using a contrast of action imitation versus action execution in response to a symbolic cue. This contrast was implemented on the basis that simulation areas are activated during action observation and execution, and maximally active during imitation as it involves both visual encoding of the action and execution (Iacoboni, 2009). This contrast also served to control for initiation of the motor plan since both conditions involved the same action. Whole-brain contrasts were thresholded at $p < .005$ and corrected for multiple comparisons to $p < .05$

(16 contiguous voxels) using AFNI's updated 3dClustSim, a spatial clustering operation with 10,000 Monte Carlo simulations on the whole brain echo-planar imaging matrix. Notably, we are mindful of recent findings regarding false-positive rates using clusterwise inference (Eklund, Nichols, & Knutsson, 2016). A threshold of $p < .005$ was reasoned to be sufficiently conservative being that we were particularly interested in the regions of overlap identified in the conjunction analyses, and reducing Type II errors as a result (Lieberman & Cunningham, 2009; Lin, Yu, Zhao, & Zhang, 2016).

Conjunction analyses were performed using the minimum statistic compared to the conjunction null (Nichols, Brett, Andersson, Wager, & Poline, 2005) to identify overlap between regions engaged during cognitive empathy (false belief > false photo) and simulation regions as identified using the simulation network localizer (imitate-video > execute-image), and emotional empathy (feeling > age estimation) and localized simulation regions, as well as across cognitive and emotional empathy, and all three conditions. Thus, the contrasts of interest were individually thresholded at $p < .005$ and corrected for multiple comparisons to $p < .05$, then overlapping areas of significant activation were determined.

Paired t-tests with Bonferroni correction were also conducted in SPSS to examine differences in percent BOLD signal change during cognitive empathy (false belief > false photo) versus emotional empathy (feeling > age estimation). To restrict the number of comparisons, this was only interrogated in significant clusters identified using the simulation network localizer (imitate-video - execute-image) that incorporated regions traditionally considered to be part of the simulation network, or mirror neuron system, including the IFG, PMC, IPL, and/or posterior STS (Grezes, Armony, Rowe, & Passingham, 2003). Lastly, correlational analyses with Bonferroni correction were utilized to identify relationships between behavioural performance on the cognitive and emotional empathy tasks and activation within the same subset of simulation clusters, as well as activity in regions of overlap identified using conjunction analyses between cognitive and emotional empathy, and the simulation network localizer. Data points falling +/- 3 SDs from the mean for extracted percent BOLD signal change for cognitive empathy and emotional empathy, in each region of interest, were identified as outliers and removed from the analyses. For accuracy on the false belief questions during the cognitive empathy task, and mean

feeling ratings during the emotional empathy task, data points falling \pm 3 SDs from the mean were also excluded from the analyses.

4.3 Results

4.3.1 Within-task effects (Table 4.1, Figure 4.2)

4.3.1.1 Cognitive empathy

The contrast of false belief trials versus false photo trials for cognitive empathy revealed significantly greater activation in bilateral temporal pole, superior temporal sulcus (STS), and temporoparietal junction (TPJ), dorsal to ventromedial prefrontal cortex (PFC), and posterior cingulate into precuneus, consistent with expectations. Alternatively, during false photo trials as compared to false belief trials, increased activity was observed in the bilateral dorsolateral PFC and IPL.

4.3.1.2 Emotional empathy

The feeling versus age estimation contrast for emotional empathy showed significantly heightened activity in areas implicated in emotional empathy (Bzdok et al., 2012), including bilateral inferior frontal gyrus (IFG) and dorsomedial PFC, as well as left premotor cortex (PMC), anterior insula, and a large area extending from the temporal pole to the posterior STS and TPJ. Age estimation in comparison to the feeling condition produced greater activation in the right dorsolateral PFC and bilateral IPL.

4.3.1.3 Simulation

The contrast of imitate-video versus execute-image conditions from the simulation network localizer task revealed greater activity in bilateral posterior STS into inferior parietal lobule (IPL) and mid occipital gyrus, bilateral IFG and PMC, as well as bilateral anterior insula, supplementary motor area (SMA), and precuneus during action imitation in comparison to action execution in response to a symbolic cue.

Table 4.1: Whole-brain within-task contrasts

Region	L/R	BA	x	y	z	t-value	Voxels	
Cognitive Empathy								
false belief > false photo								
temporal pole/STS/TPJ	R	38/21/22/39/40	54.3	2.1	-19.2	9.75	2414	
temporal pole/STS/TPJ	L	38/21/22/39	-56.8	-56.4	20.1	8.30	1946	
mPFC	L/R	9/10	-8.8	54	31.4	6.52	1605	
precuneus/posterior cingulate cortex	L/R	7/31	-1.3	-59.9	39	10.45	1217	
pyramis (cerebellum)	L		-24	-74.5	-38.6	5.77	83	
subgenual cingulate cortex/caudate	L		25	-6.3	4.2	-7.2	4.86	56
middle frontal gyrus/PMC	R		6	39.1	1.6	47.7	3.73	21
anterior cingulate cortex	L		24	-3.8	26.7	8.2	4.01	17
middle frontal gyrus	R		8	21.5	24.8	48.9	3.53	16
false photo > false belief								
IPL/postcentral gyrus	L		40/2	-56.8	-36.7	40.2	-6.24	601
dorsolateral PFC	L		46	-41.7	28.2	30.1	-5.97	470
mid/inferior temporal gyrus	L		20/37	-59.3	-41.9	-15.8	-7.08	389
dorsolateral PFC	R		46	49.2	36.4	22.3	-5.40	321
IPL/postcentral gyrus	R		40/2	41.7	-50.1	50.4	-5.14	273
mid/inferior temporal gyrus	R		20/37	56.8	-39.2	-18.7	-5.39	122
IFG	L		9	-51.8	7.4	34.4	-4.91	64
IFG	R		9/44	49.2	0.1	25.8	-4.60	50
medial frontal gyrus/SMA	R		6	6.3	-14.7	65.9	-4.62	36
paracentral lobule/SMA	L		4/6	-8.8	-32.6	62.2	-3.87	26
medial postcentral gyrus	R		2/5	11.4	-48.5	69.5	-4.60	22
precuneus	L		7	-11.4	-83.3	43.2	-3.88	20
middle frontal gyrus	L		10/46	-36.6	37.6	-5.3	-4.26	19
Emotional Empathy								
feeling > age estimation								
cuneus/lingual gyrus/R cerebellum	L/R	17/18/19	11.4	-73.7	2.9	10.91	3025	
IFG/anterior insula/temporal pole/STS/TPJ	L	44/45/47/13/ 38/21/22/39/40	-46.7	20.3	-21.2	7.74	2346	
dorsomedial PFC	L		6/8/9	-6.3	5.7	69.7	5.85	717
temporal pole/IFG	R		38/47	39.1	15	-18.5	5.31	239
IFG	R		45/47	49.2	34.8	0.5	4.29	62
middle frontal gyrus/PMC	L		6	-44.2	-4.2	61	3.76	46
inferior occipital gyrus	L		18/19	-31.6	-88.5	-12.6	3.82	43
mid STS	R		22	44.2	-29.7	-0.2	5.34	38
dorsomedial PFC	R		9	11.4	51.3	34	4.02	30
parahippocampal gyrus/fusiform gyrus	L		20/36	-39.1	-26.2	-20.9	4.02	22
middle frontal gyrus/PMC	L		6	-41.7	4.1	50.5	4.15	21
anterior cingulate cortex	R		24	8.8	15.1	34.8	3.65	19
medial/superior frontal gyrus	R		9	24	38.4	33.3	3.37	17
anterior cingulate cortex	L		32	-8.8	12.3	40.1	4.1	16
age estimation > feeling								
IPL/precuneus	R		40/39/19	46.7	-55.5	55.6	-7.84	1853
dorsolateral PFC	R		8/9/46	26.5	6.1	61.5	-8.03	1331
IPL/precuneus	L		40/19	-36.6	-77.8	35.3	-6.18	524
mid/inferior temporal gyrus	R		20/37	56.8	-23.9	-14.8	-6.82	378
precuneus	L/R		7/31	6.3	-64.9	36	-4.43	268
posterior cingulate cortex	L/R		31	3.8	-39.3	40.1	-5.9	209
superior/mid frontal gyrus/PMC	L		6	-21.5	6.4	56.1	-5.55	121
mid/inferior temporal gyrus	L		20/21	-59.3	-36.7	-15.5	-5.55	75

subgenual cingulate cortex	L	25/32	-11.4	17.3	-12.4	-4.35	41
frontal pole	R	10	24	62.5	15.5	-3.93	21
inferior semilunar lobule (cerebellum)	L/R		-6.3	-79	-53.7	-4.24	20
inferior temporal gyrus	R	37	64.4	-49.7	-13.3	-4.23	20
primary motor cortex	R	4	61.9	-18.6	38.5	-3.99	18
orbitofrontal cortex/ventromedial PFC	R	11	6.3	35.6	-17.3	-5.1	17

Simulation Network Localizer

imitate-video > execute-image

mid-posterior STS/TPJ/IPL/mid-inferior temporal gyrus/mid occipital gyrus/fusiform gyrus	R	22/37/19/39/40	51.8	-63.1	-2.2	13.7	2628
PMC/mid frontal gyrus/IFG/anterior insula	R	6/45/47/13	39.1	-6.9	63.6	5.59	1168
posterior STS/TPJ/IPL/mid temporal gyrus/mid occipital gyrus/fusiform gyrus	L	22/19/39/40	-54.3	-53.2	6.7	6.81	928
precuneus/superior-mid occipital gyrus	R	7/19	21.5	-73.3	49.2	5.55	797
medial-superior frontal gyrus/SMA	R	6	16.4	3	72.3	5.56	422
pyramis/uvula (cerebellum)	L		-16.4	-66.6	-41.1	6.66	225
superior-mid frontal gyrus/PMC	L	6	-29	-7.3	71.7	4.92	209
dorsolateral PFC	L	46	-49.2	41.4	25.3	4.49	108
anterior insula	L	13	-39.1	19.1	5.1	4.44	53
declive (cerebellum)	L		-46.7	-51.7	-28.3	4.16	44
lateral mid frontal gyrus	L	10	-44.2	52.3	12.3	4.04	42
culmen (cerebellum)	L		-29	-56.7	-31.6	4.94	32
precuneus	R	7	26.5	-49.7	42.3	3.67	32
pre/cuneus	L	7	-18.9	-80.6	40.6	4.57	31
fusiform gyrus	R	20	41.7	-20.8	-26.5	4.45	29
lateral mid frontal gyrus	R	10	34.1	43.6	33.6	4.04	29
IFG	L	9/6	-44.2	2.6	26	4.29	28
IFG	L	47/45/13	-49.2	16.9	-3.5	4	26
IPL	L	40	-59.3	-26.3	38.1	3.91	25
medial-superior frontal gyrus/SMA	L	6	-8.8	-14.9	68.6	3.94	25
orbitofrontal gyrus	R	11	21.5	25.4	-20.9	4.19	22
superior frontal gyrus	L	9	-34.1	48.5	39.3	4.08	22
superior parietal lobule/precuneus	L	7	-16.4	-73.4	51.9	4.05	18
execute-image > imitate-video							
cuneus	L/R	17/18	-16.4	-79	5.4	-4.76	178
caudate/hippocampus	R		29	-34.7	-3.5	-5	38

Thresholded at $p < .005$; $p < .05$ corrected. Table displays region (STS, superior temporal sulcus; TPJ, temporoparietal junction; PMC, premotor cortex; PFC, prefrontal cortex; SMA, supplementary motor area; IFG, inferior frontal gyrus), hemisphere (L, left; R, right), Brodmann area (BA), MNI coordinates (x, y, z), maximum neural activity for the peak of that cluster (t-value), and cluster size in voxels.

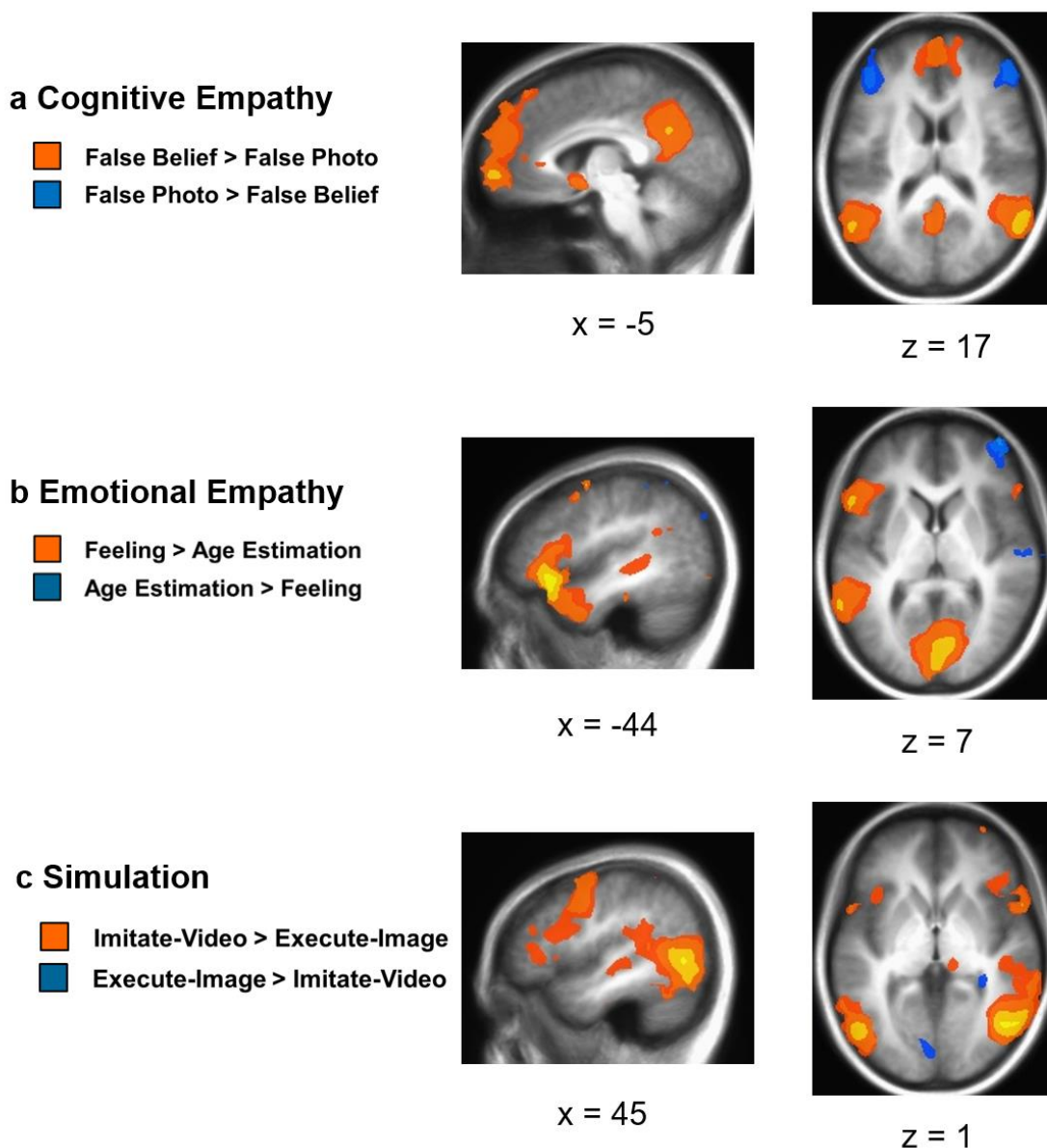


Figure 4.2 Neural regions demonstrating significant effects in within-task contrasts

Whole-brain analyses were conducted at a threshold of $p < .005$, and corrected to a family-wise error rate of $p < .05$. (a) The false belief > false photo contrast revealed greater activity in areas including bilateral STS and TPJ, medial PFC, and posterior cingulate into precuneus. False photo > false belief showed greater activity in areas including bilateral dorsolateral PFC. (b) The feeling > age estimation contrast showed greater activity in regions including bilateral IFG, anterior insula, and temporal pole, and left posterior STS and TPJ. Age estimation > feeling

revealed greater activity in regions including right dorsolateral PFC. (c) The imitate-video > execute-image contrast showed greater activity in areas including bilateral posterior STS into IPL, IFG and PMC, and anterior insula. Execute-image > imitate-video showed greater activity in bilateral cuneus and right hippocampus.

4.3.2 Conjunction analyses (Table 4.2, Figure 4.3)

4.3.2.1 Cognitive empathy and simulation

In order to identify simulation regions that were also recruited during cognitive and/or emotional empathy, conjunction analyses were conducted. Regions found to be commonly activated by the simulation network localizer (imitate-video > execute-image) and cognitive empathy (false belief > false photo) included the right mid/posterior STS and TPJ, left posterior STS and TPJ, and bilateral precuneus.

4.3.2.2 Emotional empathy and simulation

A second conjunction analysis revealed brain areas that were significantly activated both during the simulation network localizer and emotional empathic experience (feeling > age estimation), including the left posterior STS and TPJ, two regions in the SMA, the right mid STS, and left IFG.

4.3.2.3 Cognitive and emotional empathy

A conjunction of regions significantly activated during both cognitive empathy and emotional empathy identified commonly recruited regions including the left temporal pole into STS and TPJ, bilateral dorsomedial PFC, and right temporal pole and mid STS.

4.3.2.4 Cognitive empathy, emotional empathy, and simulation

The left posterior STS and right mid STS were identified as regions activated by the simulation network localizer, and both cognitive and emotional empathy.

Table 4.2: Conjunction analyses

Region	L/R	BA	x	y	z	Voxels
Cognitive Empathy and Simulation						
mid/posterior STS/TPJ	R	21/22/39	46.7	-18.9	-11.5	591
posterior STS/TPJ	L	22/39	-59.3	-42.8	4.5	199
precuneus	L/R	7	3.8	-55	44.7	18
Emotional Empathy and Simulation						
posterior STS/TPJ	L	22/39	-59.3	-47.7	-1.3	274
pre/cuneus	R	18/31	26.5	-79.2	10.8	103
superior frontal gyrus/SMA	R	6	11.4	6	64.3	27
medial frontal gyrus/SMA	L/R	6	-1.3	1.1	58.6	26
mid STS	R	21/22	46.7	-24.4	-2.9	21
IFG	L	47/45/13	-54.3	19.6	-6.3	16
Cognitive Empathy and Emotional Empathy						
temporal pole/STS/TPJ	L	38/21/22/39	-41.7	10.7	-39.6	804
dorsomedial PFC	L	9	-11.4	46.5	25.6	272
temporal pole	R	38	54.3	12.9	-30.5	162
mid STS	R	21/22	44.2	-26.8	-6	37
dorsomedial PFC	R	9	8.8	56.6	31.6	27
Cognitive Empathy, Emotional Empathy, and Simulation						
posterior STS/TPJ	L	22/39	-59.3	-42.8	4.5	158
mid STS	R	21/22	46.7	-24.4	-2.9	21

Table displays region (STS, superior temporal sulcus; TPJ, temporoparietal junction; PMC, premotor cortex; PFC, prefrontal cortex; SMA, supplementary motor area; IFG, inferior frontal gyrus), hemisphere (L, left; R, right), Brodmann area (BA), MNI coordinates (x, y, z), and cluster size in voxels.

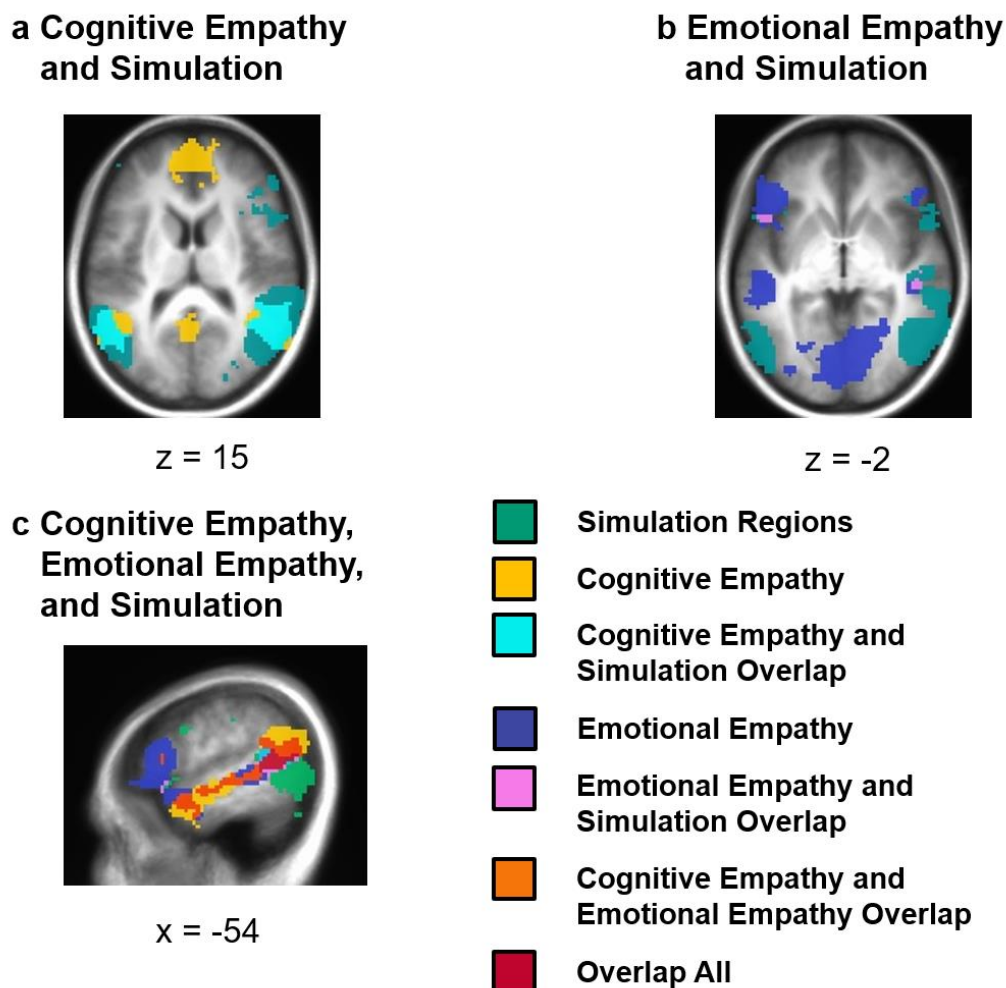


Figure 4.3 Neural regions demonstrating significant effects in conjunction analyses

(a) The conjunction of cognitive empathy (false belief > false photo) and the simulation network (imitate-video > execute-image) revealed overlap in areas including bilateral posterior STS and TPJ, and bilateral precuneus. (b) The conjunction of emotional empathy (feeling > age estimation) and the simulation network showed overlap in regions including right mid STS and left IFG. (c) The conjunction of cognitive empathy, emotional empathy, and the simulation network showed overlap in areas including left posterior STS.

4.3.3 Between-task effects

Paired t-tests were also utilized to determine whether simulation regions were significantly more active during emotional as compared to cognitive empathy. There were seven simulation clusters identified using the simulation network localizer that included our a priori regions of interest (the IFG, PMC, STS, and/or IPL; see Table 4.1). Of these regions, paired t-tests revealed that activation was significantly greater during emotional versus cognitive empathy in two clusters in the left IFG, including one in Brodmann area (BA) 9/6 [$t(34) = 3.02$, corrected $p = .035$; Figure 4.4a] and one in BA 47/45/13 [$t(34) = 3.17$, corrected $p = .021$; Figure 4.4b]. Notably, none of these clusters within the simulation network showed significantly greater activity for cognitive relative to emotional empathy. Further, one-sample t-tests revealed that activation during cognitive empathy in these clusters of interest did not differ significantly from baseline, other than the cluster in the left IPL, where activation was significantly less than baseline [$t(34) = -3.19$, corrected $p = .021$].

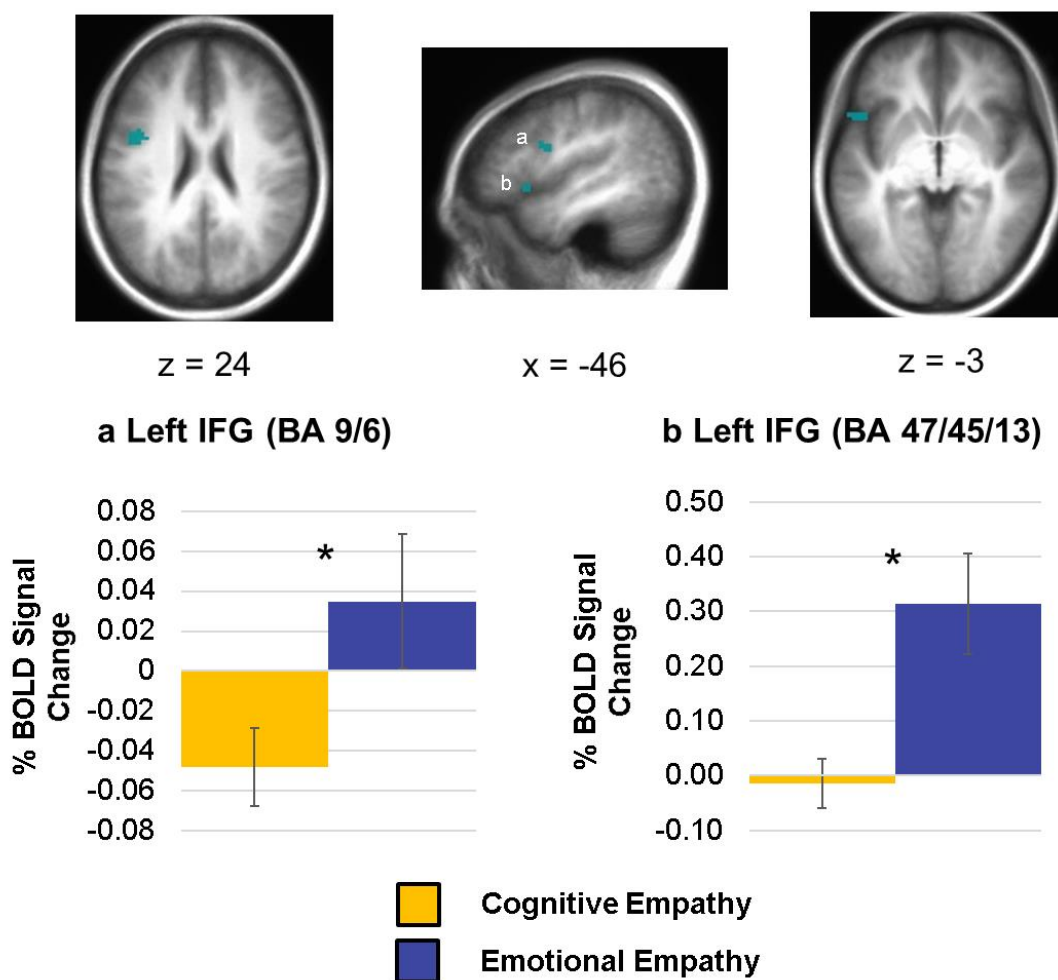


Figure 4.4 Between-task effects

Mean percent BOLD signal change during cognitive empathy (false belief > false photo) and emotional empathy (feeling > age estimation) in clusters identified using the simulation network localizer task (imitate-video > execute-image), including (a) a cluster in BA 9/6 in the left IFG and (b) a cluster in BA 47/45/13 in the left IFG. Error bars represent standard errors;

* Bonferroni corrected $p < .05$.

4.3.4 Correlational analyses with task performance

4.3.4.1 Correlations with activation in simulation regions of interest

Correlational analyses between task performance and corresponding neural activity were conducted in the same seven simulation clusters of interest (see Table 4.3). For cognitive empathy, accuracy on the false belief questions was not significantly correlated with activation during the cognitive empathy task (false belief > false photo) in any of the seven identified simulation clusters including regions of the IFG, PMC, STS, and/or IPL (all $p > .1$). For emotional empathy, a positive association was identified between mean feeling ratings in response to emotionally-charged images and activation during the emotional empathy task (feeling > age estimation) in the cluster identified in BA 47/45/13 of the left IFG ($r = .461$, corrected $p = .035$; Figure 4.5a).

Fisher z-transformation (Fisher, 1915) was performed to determine whether the correlation between mean feeling ratings and emotional empathy activation in this cluster in left BA 47/45/13 was significantly stronger than the relationship between accuracy on the false belief questions and cognitive empathy activation in this region ($r = .109$, corrected $p > .1$). This was done to test the prediction that activation in the simulation network would be associated more strongly with emotional empathy versus cognitive empathy task performance. There was a trend towards a stronger association between mean feeling ratings and emotional empathy activation than between cognitive empathy accuracy and activation within the simulation cluster identified in BA 47/45/13 of the left IFG ($z = 1.57$, $p = .058$ one-sided).

4.3.4.2 Correlations with activation in conjunction-based regions of overlap

Correlations were also utilized to determine whether cognitive or emotional empathy task performance was associated with activation in regions of overlap identified in the conjunction analyses, between simulation areas and those activated during these respective tasks. Specifically, accuracy on the false belief questions during the cognitive empathy task was not significantly associated with activation during cognitive empathy in any of the three identified

regions recruited by both the simulation network localizer and the cognitive empathy task, including right and left STS into TPJ, and bilateral precuneus. However, mean feeling ratings on the emotional empathy task were found to be positively associated with activity during emotional empathy in the region of the left inferior frontal gyrus (BA 47/45/13) recruited by both the simulation network localizer and emotional empathy tasks ($r = .437$, corrected $p = .048$; Figure 4.5b). Activation in the other five areas of overlap between emotional empathy and simulation was not associated with emotional empathy performance.

Table 4.3: Correlations between task performance and corresponding neural activity in significant clusters identified using the simulation network localizer including a priori regions of interest

	Activation during cognitive empathy (false belief > false photo)						
	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7
False belief question accuracy	0.121	0.040	0.063	-0.018	-0.029	0.109	-0.045
	Activation during emotional empathy (feeling > age estimation)						
	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7
Mean feeling ratings	0.297	0.129	0.333	0.293	0.111	0.461*	0.274

Cluster 1 - R mid-posterior STS/TPJ/IPL/mid-inferior temporal gyrus/mid occipital gyrus/fusiform gyrus

Cluster 2 - R PMC/mid frontal gyrus/IFG/anterior insula

Cluster 3 - L posterior STS/TPJ/IPL/mid temporal gyrus/mid occipital gyrus/fusiform gyrus

Cluster 4 - L superior-mid frontal gyrus/PMC

Cluster 5 - L IFG (BA 9/6)

Cluster 6 - L IFG (BA 47/45/13)

Cluster 7 - L IPL

* Bonferroni corrected $p < .05$

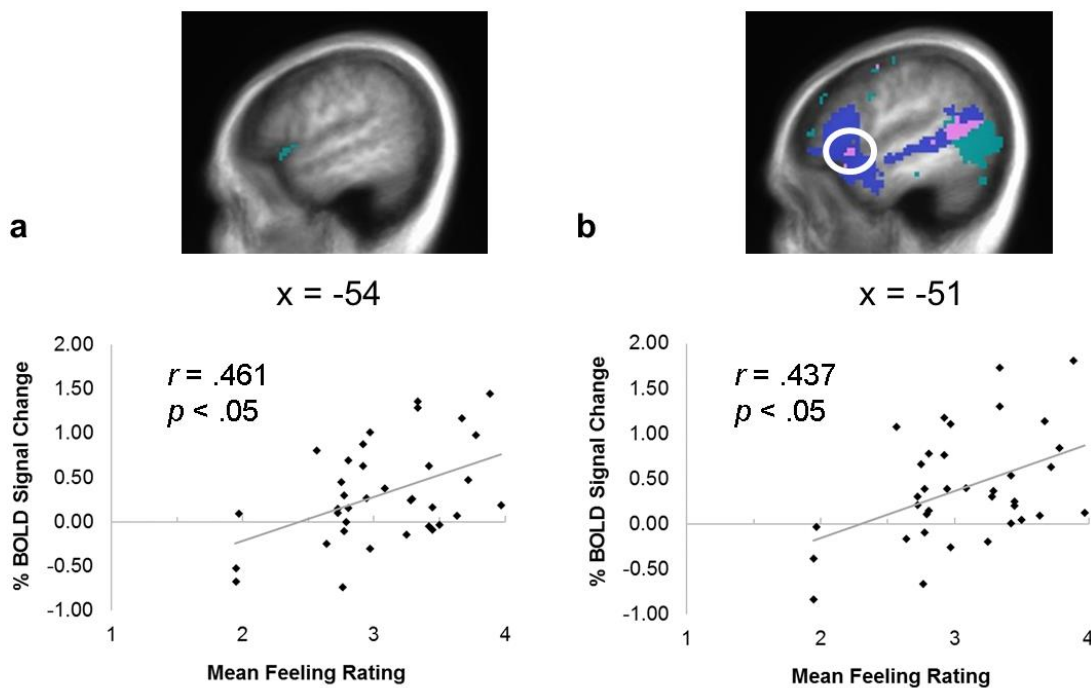


Figure 4.5 Correlational analyses with task performance

Correlations between percent BOLD signal change during emotional empathy (feeling > age estimation) and mean feeling ratings on the emotional empathy task in (a) the cluster in BA 47/45/13 in the left IFG identified using the simulation network localizer task (imitate-video > execute-image), and (b) the region of overlap (pink) in the left IFG identified in the conjunction of emotional empathy and the simulation network.

4.4 Discussion

Suggestions that simulation mechanisms underlie empathy are fairly common (Agnew, Bhakoo, & Puri, 2007; Bastiaansen et al., 2009; Gallese, 2001; Iacoboni, 2009; Molnar-Szakacs, 2011; Preston & de Waal, 2002; Wolf, Gales, Shane, & Shane, 2001), but past investigations have provided limited evidence regarding the role of the simulation network in cognitive and emotional empathy. In particular, support for this has largely relied on demonstrations of activation in regions broadly considered to be part of the simulation network during cognitive or

emotional empathy tasks, and correlations between questionnaire indices of empathy and activity in simulation regions during action observation or imitation. Crucially, no studies to date have quantitatively compared the involvement of localized simulation regions in cognitive versus emotional empathy. The present study utilized tasks tapping the simulation network, cognitive empathy, and emotional empathy during fMRI in healthy adults to address this gap in knowledge. As predicted, conjunction analyses revealed some overlap between simulation areas and those activated during cognitive empathy, as well as emotional empathy. However, overlap in localized inferior frontal simulation areas, thought to be crucially involved in action-observation matching, was only observed for emotional, and not cognitive, empathy. Critically, and in line with expectations, greater activation was also observed during emotional empathy relative to cognitive empathy in localized simulation regions in the left IFG. Indeed, activity was not found to be greater during cognitive than emotional empathy in any of the localized simulation regions of interest. Further, consistent with our predictions, within a region of overlap between emotional empathy and the simulation network in the left IFG, a positive association was demonstrated between the mean feeling ratings provided and activation during the emotional empathy task. Thus, our results suggest that simulation areas thought to be critical for observation-execution matching are preferentially involved during the experience of emotional empathy.

4.4.1 Cognitive empathy and simulation

Consistent with expectations, areas of overlap were identified between simulation regions and brain areas recruited during both cognitive and emotional empathy. More specifically, identified simulation regions that were also recruited during cognitive empathy included bilateral posterior STS extending into the TPJ, and bilateral precuneus. Studies typically identify activation in the posterior STS during both simulation (Caspers et al., 2010; Grezes et al., 2003) and cognitive empathy (Carrington & Bailey, 2009; Mar, 2011; Molenberghs, Johnson, Henry, & Mattingley, 2016) tasks. It has also been suggested that this region may act as a link between these two systems (Van Overwalle, 2009). Notably, though the posterior STS is considered part of the simulation network, it is not engaged during action execution and instead provides visual

input to the other regions (Iacoboni et al., 2001; Keysers & Perrett, 2004). Thus, the absence of common recruitment of the IFG, PMC, or IPL demonstrated presently does not provide support for the involvement of critical simulation regions, and thereby an action-perception matching mechanism, in cognitive empathy based on mental state inference from verbal information. This coincides well with demonstrated overlap in bilateral STS, as well as visual association areas and the fusiform gyri, from an fMRI investigation that directly compared neural activity during cognitive empathy and simulation (Ohnishi et al., 2004). Further, a recent meta-analysis of simulation and theory of mind investigations found that regions engaged by each were largely distinct and rarely recruited simultaneously, suggesting that these systems are complementary rather than subserving one another (Van Overwalle & Baetens, 2009). The STS responds to biological motion (Puce & Perrett, 2003) and is also thought to be involved in social perception and mental state inference (Allison, Puce, & McCarthy, 2000; Yang, Rosenblau, Keifer, & Pelphrey, 2015). Thus, the STS appears to be involved in both simulation and cognitive empathy, but it may serve to encode visual properties of actions in the simulation network, whereas it may be involved in understanding mental states requiring inference and reflective representation along with the other regions typically implicated in cognitive empathy (de Lange, Spronk, Willems, Toni, & Bekkering, 2008; Spunt et al., 2011; Yang et al., 2015). This account is consistent with our present results, as we see recruitment of typical cognitive empathy regions during belief inference, including regions of the posterior STS that are also engaged during simulation, but not other critical regions of the simulation network.

4.4.2 Emotional empathy and simulation

In the case of emotional empathy, overlap with localized simulation areas was observed in several regions. These included the left posterior STS, right middle STS, right precuneus extending into the cuneus, bilateral SMA, and the left IFG. Notably, the IFG represents a critical region of the simulation network for observation-execution matching, as it has been established as an area that contains neurons that respond to both goal-directed action observation and execution, in macaque monkeys (di Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). In humans, the IFG has also consistently been shown to

respond during both action perception and execution using fMRI (Caspers et al., 2010; Molenberghs et al., 2012), and there is compelling evidence for the existence of neurons with these properties in the left IFG from fMRI adaptation paradigms (de la Rosa, Schillinger, Bulthoff, Schultz, & Uludag, 2016; Kilner, Neal, Weiskopf, Friston, & Frith, 2009). Further, transient lesions induced using repetitive transcranial magnetic stimulation over bilateral posterior IFG has been shown to result in impaired imitation compared to stimulation of the occipital cortex (Heiser, Iacoboni, Maeda, Marcus, & Mazziotta, 2003), and patients with IFG lesions have demonstrated deficits in encoding human actions (Fazio et al., 2009). Prior investigations often identify the IFG as being significantly activated during emotional empathy tasks (Bzdok et al., 2012; Lamm et al., 2011; Shamay-Tsoory, 2011), but such investigations tend not to directly compare identified clusters with those activated during simulation tasks. Of particular relevance, a study by Nummenmaa et al. (2008) examined the neural correlates of both cognitive and emotional empathy and interpreted significant activation in the right anterior PMC (36, -12, 64) during their emotional empathy condition as involvement of the simulation network. However, this identified region was not explicitly compared to coordinates of areas identified in prior studies of simulation nor was a simulation network localizer included. Our findings corroborate the involvement of the IFG, a critical region of the simulation network, in emotional empathy. Crucially, here we provide unique confirmation of this by demonstrating overlap in recruitment between an emotional empathy and simulation task in the same sample population.

4.4.3 Emotional versus cognitive empathy and simulation

The demonstration of common recruitment of the IFG, a region thought to be critical for action-perception matching, during simulation and emotional, but not cognitive, empathy suggests that the simulation network may be more involved in the facilitation of emotional empathy. However, the presence of activation does not prove that this region is significantly more involved in emotional than cognitive empathy. Critically, we also provide quantitative evidence for this, consistent with expectations. Namely, two localized simulation clusters in the left IFG were found to be recruited to a significantly greater degree during emotional empathy in

comparison to cognitive empathy. Correlational analyses also revealed a brain-behaviour relationship that provides unique and further support for the functionality of the left IFG in emotional empathic behaviour. Specifically, within one of these clusters in the left IFG (BA 47/45/13), there was a positive association between activation during emotional empathy and mean feeling ratings on the emotional empathy task. In line with our prediction that behavioural indices of emotional empathy would be more strongly associated with activity in simulation areas than cognitive empathy, this correlation in the left IFG was marginally significantly stronger than that between activity during cognitive empathy in this region and false belief accuracy. Lastly, this association was also observed within the region of the left IFG that was commonly recruited during both emotional empathy and simulation. This marks the first time that a link has been demonstrated between emotional empathic behaviour and activity in an independently localized simulation region also recruited during emotional empathy. These findings corroborate demonstrations of positive relationships between questionnaire measures of emotional, but not cognitive, empathy, and IFG activation during a facial emotional observation and imitation task (Pfeifer et al., 2008), as well as gray matter volume in the right IFG (Cheng et al., 2009). Further, this is consistent with prior work showing emotional empathy deficits, but intact cognitive empathy, in patients with IFG lesions (Shamay-Tsoory et al., 2009). These results provide compelling evidence that the simulation network is preferentially involved in emotional empathy, and that the IFG may be a particularly important simulation region for emotional empathic responding.

4.4.4 Mechanisms of simulation in emotional empathy

Our findings provide strong evidence for a role of critical regions of the simulation network in emotional empathy. However, areas found to be significantly activated during emotional empathy extended beyond the simulation network, as in previous investigations (Bzdok et al., 2012; Fan et al., 2011), and the question remains as to how the simulation network interacts with these other neural regions to elicit emotional empathy. It has been suggested that the anterior insula may act as a critical link between action representation in the simulation network and emotion representation in the limbic system to modulate empathic experience (Carr

et al., 2003; Molnar-Szakacs, 2011; Pfeifer & Dapretto, 2009; Preston & de Waal, 2002). The insula is situated between the IFG and regions of the limbic system, such as the amygdala, and anatomical data suggest that its dysgranular field is connected to the inferior frontal, posterior parietal, and superior temporal cortices, as well as the limbic system (Augustine, 1996). Increased activation found in the IFG and ventral PMC, the anterior insula, and the amygdala during the observation and imitation of emotional facial expressions has been taken to provide support for the insula acting as a relay between action and emotion representation (Carr et al., 2003; Dapretto et al., 2006; Leslie et al., 2004). Further, Granger causality has been utilized to demonstrate functional connectivity from BA 45 of the IFG to a region including the anterior insula during the observation of emotional expressions, reflecting a causal link between motor simulation and emotional simulation (Jabbi & Keysers, 2008). This coincides with the present findings being that the area of the IFG engaged during both our simulation and emotional empathy tasks was localized on the boundaries of BA 45 and the anterior insula. During emotional empathy, activation was also elicited in the anterior insula, as well as the anterior cingulate cortex, a region of the limbic system.

This account is also particularly interesting given that humans show an unconscious drive to imitate facial expressions in others (Dimberg, Thunberg, & Elmehed, 2000). Such emotional mimicry could reflect an overt behavioural form of emotional resonance, parallel to this more covert neural matching mechanism instantiated by the simulation network during observation (Jabbi & Keysers, 2008), that may also generate neural activity in simulation and emotional regions to influence emotional responding. Indeed, stronger facial mimicry in response to emotional scenes has been linked with reports of heightened shared emotional experience (Van der Graaff et al., 2016), as well as greater emotional empathy questionnaire scores (Balconi, Bortolotti, & Crivelli, 2013). Further, a positive correlation has been shown between imitation accuracy and activation in both the insula and PMC during imitation of emotional faces, as well as between empathy scores and premotor activity during imitation (Braadbaart, de Grauw, Perrett, Waiter, & Williams, 2014). These findings are compatible with ours and support the suggestion that the mechanism underlying emotional empathic responding may involve emotional resonance by way of an interaction between the simulation network and the limbic system via the insula.

4.4.5 Roles of additional regions of overlap

Notably, the left posterior STS and middle right STS were identified as the only regions commonly recruited during simulation, cognitive empathy, and emotional empathy. The STS is involved in the perception of biological movement in both humans and monkeys (Allison et al., 2000; Puce & Perrett, 2003). It is also believed to be involved in the processing of static and dynamic social stimuli, as well as temporal integration of information and intention understanding (Bahnemann, Dziobek, Prehn, Wolf, & Heekeren, 2010; Barraclough, Xiao, Baker, Oram, & Perrett, 2005; Yang et al., 2015). Within the simulation network, it is thought to provide visual input to the IPL and IFG (Iacoboni et al., 2001). Accordingly, a recent meta-analysis confirms that the posterior STS is the common region recruited by theory of mind, social perception, and action observation paradigms, also demonstrating that it is functionally connected to areas in these respective neural networks (Yang et al., 2015). It was suggested that the posterior STS is involved in the temporal integration of social cues and decoding basic intention from behaviour, and that this information is then relayed to downstream regions in these theory of mind, social perception, and action observation systems (Yang et al., 2015). Our results align with these findings and provide further support for a role of the STS in each of these processes.

We also found that the bilateral precuneus was commonly engaged during simulation and cognitive empathy, and a region of the right precuneus was commonly recruited during simulation and emotional empathy. This coincides with the postulation that cortical midline structures such as the precuneus interact with simulation regions due to their mutual involvement in self-other representations (Uddin, Iacoboni, Lange, & Keenan, 2007). Notably, it is believed that simulation regions are more involved in physical representations of the self (Uddin, Kaplan, Molnar-Szakacs, Zaidel, & Iacoboni, 2005), whereas the precuneus is likely to be more involved in mental representations (Uddin et al., 2007).

Of additional note, the bilateral SMA was also commonly recruited during simulation and emotional empathy. The SMA is involved in motor control and action preparation, and a meta-analysis has demonstrated its consistent activation during action observation, execution, and

mental simulation (Grezes & Decety, 2001). Indeed, single-cell recording in humans has revealed neurons that respond during both action execution and observation in the SMA (Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010). It has also been identified as a region activated across empathy paradigms in a recent meta-analysis (Fan et al., 2011). Based on the demonstration of a positive correlation between SMA activation during the observation of another's pain and emotional empathy scores, it has been suggested that such SMA activation may be the result of internal simulation and resultant priming of associated responses (Lamm, Batson, & Decety, 2007).

4.4.6 Cognitive empathy, action understanding, and simulation

Despite the lack of evidence provided here for a role for the simulation network in cognitive empathy, it is important to consider the potential that simulation could be implicated in particular types or components of cognitive empathy. Specifically, prior work has suggested that cognitive empathy tasks involving the perception of movement, facial or bodily expressions, and action-based intention understanding in particular may engage the simulation network to a greater degree than those involving more abstract intentions (Gobbini, Koralek, Bryan, Montgomery, & Haxby, 2007; Iacoboni et al., 2005; Kaplan & Iacoboni, 2006; Pineda & Hecht, 2009; Schurz et al., 2014; Van Overwalle, 2009). However, opinions and results are mixed (Gallese & Goldman, 1998; Goldman & Sebanz, 2005; Kobayashi, Glover, & Temple, 2007; Pineda et al., 2009; Saxe, 2005; Spunt et al., 2011), and we chose to utilize the false belief task for our cognitive empathy paradigm because it is a classic test of theory of mind and a reliable and well-validated localizer (Dodell-Feder et al., 2011; Dufour et al., 2013). In addition, cognitive empathy is also believed by some to include both cognitive (inference of beliefs and intentions) and affective (inference of feelings) components (Shamay-Tsoory & Aharon-Peretz, 2007). Thus, the exclusion of affective components allowed for optimal distinction between cognitive and emotional empathy components. Future studies incorporating different varieties of cognitive empathy tasks would be beneficial in elucidating this.

4.4.7 Implications for disorders featuring empathy impairments

The present findings could have important implications for clinical populations that feature debilitating deficits in specific facets of empathic responding. More specifically, the simulation network may be of particular interest in disorders featuring emotional empathy impairments. Individuals with psychopathy and conduct disorder typically present with emotional empathy impairments but intact cognitive empathy, whereas patients with autism spectrum disorder have been found to demonstrate the opposite pattern (Blair, 2005; Dziobek et al., 2008; Jones, Happe, Gilbert, Burnett, & Viding, 2010; Schwenck et al., 2012). Alternatively, schizophrenia (Derntl et al., 2009; Green et al., 2015) and behavioural variant frontotemporal dementia (Baez et al., 2014; Lough et al., 2006; Oliver et al., 2015) appear to be characterized by deficits in both cognitive and emotional empathy (see Chapter 2.). Accordingly, it has been suggested that dysfunction in the simulation network may underlie social cognitive deficits in some of these patient populations. For example, individuals with psychopathy have shown reduced spontaneous activation in functionally and anatomically defined simulation regions, including the ventral PMC, during the observation of emotional hand interactions (e.g., loving and painful interactions) compared to healthy controls (Meffert, Gazzola, den Boer, Bartels, & Keysers, 2013). As well, a recent review illustrates that multiple investigations have found diminished activity in simulation network regions, including the IFG, ventral PMC, and IPL in patients with schizophrenia during motor and social tasks (Mehta et al., 2014). This raises the possibility that emotional empathy impairments in these patient populations may be associated with simulation network dysfunction. It should also be noted that a deficit in the simulation network has been postulated to underlie social cognitive impairments in autism spectrum disorder (Iacoboni & Dapretto, 2006; Williams, Whiten, Suddendorf, & Perrett, 2001). However, evidence for this account is mixed and alternative explanatory models have been suggested (Hamilton, 2013; Hamilton, Brindley, & Frith, 2007), such that this does not necessarily contradict our findings regarding a greater role for the simulation network in emotional than cognitive empathy. Thus, there is some support for simulation network dysfunction in disorders featuring emotional empathy impairments, but the demonstration of a causal link between these elements is still required to determine whether treatments or compensatory options targeting the simulation network, such as imitation or action observation interventions (Iacoboni & Mazziotta, 2007), would be beneficial.

In relation to this, our findings suggest that the experience of emotional empathy involves the simulation network, and thereby that simulation of the perceived experience in others influences emotional empathy, but we cannot conclude that simulation mechanisms are necessary for emotional empathy. However, the demonstration of emotional empathy impairments in patients with IFG lesions including anatomically defined simulation areas (Shamay-Tsoory et al., 2009) supports this idea. Notably, if simulation mechanisms are necessary for emotional empathy, it does not follow that they are sufficient. For example, lesions to the insula have also been found to result in emotional empathy deficits (Driscoll, Dal Monte, Solomon, Krueger, & Grafman, 2012; Gu et al., 2012). Further, it has been suggested that action-perception matching mechanisms may be essential for certain aspects of emotional empathy, and sharing the emotional experience of another individual (affective sharing) in particular, but that top-down mechanisms may also influence emotional empathic experience (Balconi & Bortolotti, 2012; Decety & Jackson, 2004; Decety & Meyer, 2008; Preston & de Waal, 2002; Tousignant, Eugene, & Jackson, 2016). The complexity of these proposed relationships highlights the need for additional work focused on their elucidation, and how this is linked to the manifestation of empathy impairments.

4.4.8 Limitations and future directions

Although the empathy tasks presently utilized included behavioural measures of both cognitive and emotional empathy, it should be noted that there could be an issue concerning measurement. Namely, it is possible that the difference identified between correlations for emotional empathy activation and mean feeling ratings versus cognitive empathy activation and accuracy on the false belief task was a result of the feeling ratings being a better measure of performance than false belief accuracy. Though participants did not perform at ceiling on the false belief task, they did perform quite well with limited variability, which may have reduced the possibility of identifying correlations with this measure. However, the spread of feeling ratings provided during the emotional empathy task appeared to be quite similar (see 4.2.2 fMRI tasks for details). The use of an alternative cognitive empathy task in future investigations may serve to clarify this. Similarly, as mentioned, future studies investigating the role of the

simulation network in different aspects of cognitive empathy, and action understanding in particular, would assist in the elucidation of whether simulation is involved in particular types of cognitive empathy or when certain stimuli are used. In relation to this, the simulation network localizer and emotional empathy tasks both included biological images, whereas the type of visual stimuli presented in the cognitive empathy task differed substantially. However, the respective control conditions were matched for visual input, such that these differences should not be driving our results. As well, incorporating an emotional simulation paradigm, such as a facial expression imitation task, versus a purely motor simulation task, such as that used presently, could be useful to further examine the interaction between the simulation network and the limbic system during emotional empathy. Lastly, more work is needed to determine whether patient populations characterized by emotional empathy impairments demonstrate deficits in the simulation network, and if these are causally associated.

4.5 Conclusions

The present work uniquely determined the correspondence between brain areas recruited during cognitive and emotional empathy, and those identified as having simulation properties, within the same participant population. Critically, this allowed for the quantitative comparison of the involvement of the simulation network in cognitive versus emotional empathy. The use of behavioural measures also provided insight into the relationship between the online experience of empathy and activation in localized simulation areas. This marks the first time that an investigation has utilized a localizer to define simulation regions along with a behavioural index of cognitive and emotional empathy. Overall, our findings provide strong evidence for greater involvement of simulation mechanisms in emotional empathy than cognitive empathy. More specifically, our results demonstrated common recruitment of a critical simulation area for observation-execution matching, the IFG, during simulation and emotional empathy, but not cognitive empathy. In addition, we uniquely determined that localized simulation regions in the IFG were recruited to a greater degree during emotional than cognitive empathy. Lastly, correlational analyses demonstrated a functional link between activation during emotional empathy in inferior frontal simulation areas and the degree of emotional empathy expressed

during the task. These findings suggest that simulation mechanisms are preferentially involved in emotional empathy, providing unique insight into the nature of empathy and daily interpersonal interactions. Further, the simulation network may be of particular interest in disorders featuring emotional empathy impairments.

4.6 References

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Chapter 5

5 Discussion

The three studies comprising this thesis provide unique insight into the dissociability, influential factors, and neural mechanisms of cognitive empathy, and emotional empathy, including affective sharing and empathic concern. In combination, they exemplify a multifaceted approach which includes between-group contrasts of behavioural data in patients with empathy dysfunction and healthy controls, as well as individual differences, and functional neuroimaging approaches in the healthy population. Taken together, these findings support our central hypothesis that cognitive empathy, affective sharing, and empathic concern represent aspects of empathy that are distinguishable and differentially linked with certain patient populations, subclinical traits, and neurocognitive mechanisms.

In Study I, investigating empathic responding to both negative and positive emotionally-charged social images in patients with behavioural variant frontotemporal dementia (bvFTD) provided novel information about the specificity of the empathy deficits seen in this patient population, which also served to inform our fundamental conceptualization of empathy and its components. More specifically, patients with bvFTD demonstrated a global cognitive empathy impairment in the form of reduced mental state inference accuracy for both negative and positive states relative to healthy controls. Patients also exhibited diminished affective sharing selectively for negative experiences, but expressed similar levels of empathic concern as controls in response to negative and positive social images. Lastly, less negative emotional reactions were demonstrated in response to negative context-only images in patients with bvFTD in comparison to healthy controls, and covariate analyses revealed that this may have contributed to the observed affective sharing deficits. These findings confirmed our prediction that aspects of empathy can be differentially affected in patient populations featuring empathy deficits.

Given that empathy has been inversely associated with aggressive, antisocial behaviour (Miller & Eisenberg, 1988), and offending (Eisenberg, Eggum, & Di Giunta, 2010; Jolliffe & Farrington, 2004), differences in empathic abilities even within the healthy population may have pronounced social effects and be costly to society. Thus, following the demonstration of differential deficits in components of empathy in bvFTD in Study I, we were interested in determining whether individual differences in specific traits linked with disorders characterized

by empathy impairments, including psychopathic, autistic, and anxious traits, would be differentially associated with aspects of empathy in a community sample. Accordingly, using the same task as Study I in a sample of healthy adults, Study II revealed an association between increased coldhearted psychopathic traits and both dampened affective sharing and empathic concern, but not cognitive empathy accuracy. We were particularly interested in coldhearted traits because they reflect the core affective features of psychopathy, including a lack of empathy and callousness towards others (Lilienfeld & Widows, 2005). Though a significant relationship was not identified between autistic traits and levels of affective sharing or empathic concern experienced, as predicted, they were also unrelated to cognitive empathy accuracy. Lastly, higher trait anxiety was found to be positively correlated with increased affective sharing, and subjective arousal in particular. However, arousal in response to contextual rather than social aspects of the stimuli appeared to be driving this relationship. There was also little evidence for an association between empathic concern and trait anxiety levels. Thus, as predicted, differential relationships were identified between cognitive empathy, affective sharing, and empathic concern, and psychopathic, autistic, and anxious traits in the healthy population, providing further evidence that these components are distinguishable.

Studies I and II provided evidence consistent with cognitive empathy and aspects of emotional empathy being separable in both individuals featuring empathy dysfunction and the healthy population, respectively. Despite support from a range of methodologies suggesting that cognitive and emotional empathy facets are separable, it remains contentious whether they involve some similar underlying neurocognitive mechanisms. Specifically, it has been suggested that embodied simulation of perceived experience in others, via action-perception neural matching mechanisms, may facilitate cognitive and/or emotional empathy. However, the degree to which simulation is implicated in these different facets remains unclear, and the involvement of the simulation network in cognitive versus emotional empathy has not been quantitatively compared. Thus, in Study III we investigated the involvement of simulation mechanisms in cognitive versus emotional empathy using a simulation network localizer task, as well as tasks tapping cognitive empathy and emotional empathy during functional magnetic resonance imaging (fMRI) in healthy adults. Critically, conjunction analyses revealed common recruitment of the inferior frontal gyrus (IFG), a region thought to be critical for execution-observation matching, during both simulation and emotional, but not cognitive, empathy. Further, identified

simulation regions in the left IFG were recruited to a significantly greater degree during emotional as compared to cognitive empathy. These findings strongly suggest that simulation mechanisms are more involved in emotional than cognitive empathy, further elucidating the dissociability of these facets of empathy.

5.1 Further Insight into Cognitive and Emotional Empathy

As mentioned, there is an abundance of evidence providing support for cognitive and emotional empathy being distinguishable. Indeed, lesion (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009) and behavioural data (Jones, Happe, Gilbert, Burnett, & Viding, 2010; Lockwood, Bird, Bridge, & Viding, 2013; Schwenck et al., 2012) have demonstrated a double dissociation between these two facets. Recently, gray matter density has also been differentially associated with questionnaire measures of cognitive and emotional empathy in the medial prefrontal cortex (PFC) and insula, respectively (Eres, Decety, Louis, & Molenberghs, 2015). Our behavioural findings from Study I coincide with this, as patients with bvFTD presented with differential deficits in cognitive versus emotional aspects of empathy. Further, in Study II, greater coldhearted psychopathic traits in healthy adults showed a selective association with decreased emotional, but not cognitive, empathy levels. Coldheartedness was also found to be more strongly related to empathic concern ratings than cognitive empathy performance. Lastly, and most critically, in Study III we provided the first quantitative evidence for greater involvement of the simulation network during emotional empathy as compared to cognitive empathy, demonstrating a greater role for simulation mechanisms in emotional empathic experience. We also identified, for the first time, a positive correlation between online emotional empathic experience and activation in a localized simulation region in the left IFG, suggesting that this area may be particularly important for emotional empathic responding. Further, greater activation was not observed for cognitive relative to emotional empathy in any of the localized simulation regions of interest. These results uniquely support and expand on prior work revealing a positive relationship between questionnaire measures of emotional, but not cognitive, empathy and IFG activation during a facial simulation task (Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008), as well as the demonstration of emotional empathy deficits but intact cognitive empathy

in patients with IFG lesions (Shamay-Tsoory et al., 2009). Thus, we provide novel insight into the mechanisms underlying cognitive and emotional empathy consistent with their distinction.

5.2 Dissociability of Affective Sharing and Empathic Concern

Affective sharing and empathic concern are believed by many to be distinguishable phenomena (Decety & Cowell, 2014; Hatfield, Rapson, & Le, 2009; Singer & Klimecki, 2014; Zaki & Ochsner, 2012). Affective sharing pertains to sharing the affective experience of another individual, whereas empathic concern refers to the motivation to care for another's welfare, including feelings of concern and compassion. However, prior work often does not discriminate between affective sharing and empathic concern components of empathy, using the term emotional empathy to refer to either (Decety, 2009; Vossen, Piotrowski, & Valkenburg, 2015). This is an important distinction to make given that they may be linked to different behavioural outcomes. Critically, here we provide behavioural evidence suggesting that affective sharing and empathic concern are at least partially dissociable. More specifically, in Study I patients with bvFTD were found to show an impairment in affective sharing for negative images but expressed a similar degree of empathic concern for negative and positive images in comparison to healthy controls. Canonical correlation results from Study II also revealed an association between higher trait anxiety levels in healthy adults and greater affective sharing, which appeared to be driven by arousal to contextual elements of the stimuli. In contrast, there was little evidence for a link between heightened trait anxiety and increased empathic concern. Further, the inverse relationship between coldhearted psychopathic traits and empathic concern was found to be stronger than the association between trait anxiety and empathic concern. The demonstration of a differential deficit in affective sharing and empathic concern in bvFTD and a relatively selective association between trait anxiety and affective sharing supports the notion that these are distinguishable components of empathic responding.

Consistent with these findings, recent factor analyses including different self-report empathy measures found that affective sharing and empathic concern loaded on distinct factors consistently (Jordan, Amir, & Bloom, 2016). Further, functional imaging investigations have provided some evidence suggesting that affective sharing and empathic concern may be

subserved by partially distinct neural substrates (Decety & Michalska, 2010; Klimecki, Leiberg, Ricard, & Singer, 2014), with traditional regions including the anterior insula, anterior cingulate cortex, and IFG involved in affective sharing (Lamm, Decety, & Singer, 2011), and regions including the ventromedial PFC, anterior cingulate cortex, and ventral striatum being particularly implicated in empathic concern (FeldmanHall, Dalgleish, Evans, & Mobbs, 2015; Klimecki, Leiberg, Lamm, & Singer, 2013). In addition, recent data from an electroencephalography study revealed that affective sharing in response to distress cues was associated with an early automatic response, whereas empathic concern modulated a later controlled response, providing evidence for the differentiation of these components at a physiological level (Decety, Lewis, & Cowell, 2015).

However, it should be noted that a marginally significant positive correlation was demonstrated between behavioural measures of affective sharing for negative stimuli and questionnaire measures of empathic concern in Study I, which suggests that affective sharing and empathic concern are not orthogonal constructs. Further, in Study II, bivariate correlational analyses demonstrated that the Multifaceted Empathy Test (MET) affective sharing and empathic concern ratings were positively associated with one another. This provides some support for our inclusion of affective sharing and empathic concern aspects under the facet of emotional empathy in our conceptualization of empathy. Though more work is needed to further characterize and delineate affective sharing and empathic concern, our results are consistent with these being partially dissociable but related constructs.

5.3 Links to Behavioural Outcomes

As mentioned, one of the motivating factors for distinguishing between affective sharing and empathic concern is that they may be associated with different behavioural outcomes. Specifically, evidence suggests that empathic concern is associated with prosocial and altruistic behaviours to relieve the stress of another individual (Batson, Duncan, Ackerman, Buckley, & Birch, 1981). In contrast, personal distress refers to feelings of discomfort and anxiety elicited in response to another individual's distress, which has been linked to the desire to relieve one's own stress rather than others' (Batson, 1991; Batson, Fultz, & Schoenrade, 1987; Eisenberg, Fabes, &

Spinrad, 2006). Personal distress is thought to be akin to emotional contagion by some (Dziobek et al., 2008; Rankin, Kramer, & Miller, 2005), which raises the possibility that it may align with affective sharing for negative situations (Singer & Klimecki, 2014). Indeed, increased levels of negative affect have been reported in response to videos of human suffering following training in affective sharing (Klimecki et al., 2014). Accordingly, our results from Study II could suggest that greater coldheartedness in the healthy population may be associated with both decreased prosocial behaviour and personal distress reactions to another's distress, based on its demonstrated association with reduced empathic concern and affective sharing. In contrast, heightened trait anxiety may have fewer implications for influencing altruistic behaviour, being that it was only weakly related to greater empathic concern. Instead, it may be associated with increased personal distress, given the demonstrated association between trait anxiety and affective sharing potentially driven by arousal, and evidence suggesting that personal distress is associated with greater levels of physiological arousal than empathic concern (Eisenberg & Eggum-Wilkens, 2009; Eisenberg et al., 2006; Eisenberg, Valiente, & Champion, 2004).

5.4 Additional Factors Affecting Empathic Responding

Interestingly, results from Study I also suggest that the representation of affective sharing may differ according to valence. Specifically, patients with bvFTD were found to demonstrate a deficit in affective sharing particularly for negative emotional states. This coincides well with some evidence for a selective impairment in recognizing negative emotional expressions in bvFTD with intact recognition of happy faces (Fernandez-Duque & Black, 2005; Kipps, Mioshi, & Hodges, 2009). These deficits in affective sharing and emotion recognition for negative, but not positive, stimuli may be due to greater degeneration of regions involved in processing negative emotions (Kumfor & Piguet, 2012). Negative emotions such as fear and disgust appear to be represented more focally in the brain (Adolphs et al., 1999; Calder, Keane, Manes, Antoun, & Young, 2000; Hennenlotter et al., 2004), whereas processing happy expressions may be represented more diffusely (Breiter et al., 1996; Fusar-Poli et al., 2009; O'Doherty et al., 2003; Phillips et al., 1998). If the experience of negative versus positive emotions is indeed dependent on partially dissociable networks, then the embodied simulation of an observed negative versus

positive affective experience of another individual should similarly involve the activation of at least a subset of these same valence-specific regions. Thus, evidence for the involvement of simulation mechanisms in emotional empathy from Study III provides support for the notion that the sharing of another's emotions might engage different brain areas according to valence, just as the experience of these emotions appears to. Indeed, a recent fMRI investigation that included empathy for pain, anxiety, and happiness conditions, has demonstrated that empathy for negative versus positive emotions respectively elicits activation in brain areas linked to negative and positive affect (Morelli, Rameson, & Lieberman, 2014). Notably, critical simulation network regions, including the IFG and inferior parietal lobule, are believed to be involved in triggering such affective simulation in additional regions via the insula (Bastiaansen, Thioux, & Keysers, 2009).

5.5 Implications for Clinical Populations Featuring Empathy Dysfunction

The findings from Study I provide greater insight into the nature of the empathy deficits associated with bvFTD. In particular, though a cognitive empathy deficit is well-established in bvFTD, we uniquely demonstrated an impairment in inferring both negative and positive mental states of others. As well, patients with bvFTD expressed reduced affective sharing for people in negative, but not positive, situations, suggesting that they show a deficit in sharing the negative emotions of other individuals. This is consistent with findings of reduced physiological responding, subjective emotional responding, and facial displays of emotion in patients with bvFTD as compared to controls during a disgust-eliciting video (Eckart, Sturm, Miller, & Levenson, 2012). In contrast, patients were found to express similar levels of empathic concern to healthy controls in response to both negative and positive social images. Notably, prior studies utilizing questionnaire measures (Eslinger, Moore, Anderson, & Grossman, 2011; Lough et al., 2006; Rankin et al., 2006) and more recent investigations using a behavioural paradigm (Baez et al., 2014; Baez et al., 2016) have demonstrated a deficit in empathic concern in bvFTD. With regard to our discrepant findings, it may be the case that the use of a more explicit question regarding concern or happiness for others in the MET allowed patients to better discern what a socially appropriate response was. However, it is of interest that empathic concern ratings on the

MET were found to be positively correlated with questionnaire scores of empathic concern in the patient group. Interestingly, a study recently found that patients with bvFTD could comply with basic social norms such as fairness, and exhibited a tendency towards prosocial behaviour (O'Callaghan et al., 2016). Patients nonetheless demonstrated significantly diminished prosocial responding in comparison to healthy controls, which the authors attributed to a deficit in integrating contextual factors in bvFTD (O'Callaghan et al., 2016). In relation to this, we observed abnormal affective responding to negative context-only stimuli in our bvFTD group, which may have contributed to their affective sharing deficits. This raises the possibility that our sample of patients with bvFTD possessed the capacity to express concern for others if directly asked, but that there may still be a disconnect between this capacity and prosocial behaviours due to contextual processing impairments. This disparity may be similar to the striking demonstration of patients with ventromedial PFC lesions expressing that they knew which decks were advantageous to choose from in a gambling task, but nonetheless continuing to make disadvantageous choices (Bechara, Damasio, Tranel, & Damasio, 1997).

Being that Study II was conducted in healthy individuals, extrapolating results regarding links between empathic responding and psychopathic trait levels to clinical populations proves difficult (e.g., Blair, 2013). Nonetheless, few investigations examining either subclinical or clinical psychopathic traits have included measures of both affective sharing and empathic concern, such that our findings are particularly informative. Presently, increased coldhearted psychopathic traits in a community sample were found to be associated with both reduced affective sharing and empathic concern. This coincides with another investigation that identified an inverse association between callous affect in healthy adults and both of these aspects of empathy (Lishner, Hong, Jiang, Vitacco, & Neumann, 2015). Given that affective sharing and empathic concern may have partially dissociable neural substrates and different underlying mechanisms, confirming whether both aspects are also affected in clinical psychopathy is of particular interest to inform potential treatment or compensatory options.

More generally, the findings from Study III suggest that the simulation network may be of particular interest in disorders featuring emotional empathy deficits. Indeed, some studies have attempted to determine whether the simulation network is dysfunctional in such patient populations. For example, an investigation has demonstrated diminished spontaneous activity in

simulation regions during the observation of loving and painful hand interactions in individuals with psychopathy (Meffert, Gazzola, den Boer, Bartels, & Keysers, 2013), and several investigations have identified reduced activation in simulation regions during motor and social tasks in patients with schizophrenia (Mehta et al., 2014). This implies that simulation network dysfunction could contribute to emotional empathy deficits in these clinical populations. However, identifying whether there is a causal link between these variables is necessary to determine whether treatments designed to target simulation mechanisms, such as interventions based on imitation (Iacoboni & Mazziotta, 2007), might be of assistance. Further, establishing an underlying deficit in the simulation network would provide insight into the level at which an empathic impairment is occurring. More specifically, simulation mechanisms are thought to be bottom-up processes, which occur automatically at the level of incoming perceptual or sensory stimuli, rather than implying a deficit in higher-level top-down modulatory processes (Decety & Meyer, 2008; Decety & Moriguchi, 2007; Dvash & Shamay-Tsoory, 2014; Preston & de Waal, 2002).

5.6 The Conceptualization of Empathy

Taken together, our results support a model of empathy including separable cognitive and emotional empathy facets, as well as at least partially dissociable components of emotional empathy, including affective sharing and empathic concern (Bernhardt & Singer, 2012; de Waal, 2008; Decety & Cowell, 2014; Decety & Jackson, 2004; Hatfield et al., 2009; Preston & de Waal, 2002; Zaki & Ochsner, 2012). Our findings are also consistent with the notion that both bottom-up and top-down processing contribute to empathic experience (Decety & Moriguchi, 2007; Preston & de Waal, 2002; Shamay-Tsoory, 2011; Singer & Lamm, 2009; Tousignant, Eugene, & Jackson, 2016). As mentioned, bottom-up processing is thought to be automatically elicited in response to sensory or perceptual information, whereas top-down processing involves incorporating the motivations, intentions, and self-regulation of an individual and moderating the degree of empathic responding (Decety & Meyer, 2008; Decety & Moriguchi, 2007). Specifically, our findings from Study III suggest that simulation mechanisms, a form of bottom-up processing, are particularly important for emotional empathy, though they cannot provide

evidence that they are necessary. However, lesion data does support a critical role for the IFG (Shamay-Tsoory et al., 2009), as well as the insula (Driscoll, Dal Monte, Solomon, Krueger, & Grafman, 2012; Gu et al., 2012), in emotional empathy, suggesting that simulation mechanisms may be necessary but are likely not sufficient for emotional empathy. With regard to how the simulation network is involved in the generation of emotional empathy, it has been proposed that the anterior insula may act as a critical link between action representation in the simulation network via the IFG and emotion representation in areas of the limbic system, such as the amygdala, to modulate empathic experience (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Molnar-Szakacs, 2011; Pfeifer & Dapretto, 2009; Preston & de Waal, 2002). Of particular note, this account is supported by the demonstration of a causal link between BA 45 of the IFG in the simulation network and a region including the anterior insula during emotional expression observation (Jabbi & Keysers, 2008). This is consistent with our findings from Study III, as the IFG cluster recruited during both simulation and emotional empathy was located on the boundaries of these two areas.

Our findings from Study III also suggest that cognitive empathy relies less on simulation mechanisms than emotional empathy. Indeed, cognitive empathy was not found to commonly activate simulation regions thought to be critical for execution-observation matching. Notably, the cognitive empathy task utilized in Study III involved mental state inference from verbal information. Thus, it may be the case that top-down processing, or higher-level deliberate cognitive processing, including perspective-taking, is more important for this aspect of cognitive empathy (Decety & Jackson, 2004; Decety & Meyer, 2008; Preston & de Waal, 2002; Tousignant et al., 2016). It is also possible, as suggested by prior work, that simulation mechanisms contribute to cognitive empathy in situations involving action-based or visual stimuli, and action-based intention understanding in particular (Gobbini, Koralek, Bryan, Montgomery, & Haxby, 2007; Iacoboni et al., 2005; Kaplan & Iacoboni, 2006; Pineda & Hecht, 2009; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014; Van Overwalle, 2009).

With regard to affective sharing versus empathic concern, it has been suggested that action-perception matching mechanisms may be particularly important for affective sharing, but that additional top-down mechanisms, such as emotion regulation and effortful control, may also contribute to emotional empathic experience (Balconi & Bortolotti, 2012; Decety & Jackson,

2004; Decety & Meyer, 2008; Preston & de Waal, 2002; Tousignant et al., 2016). The findings from Study III cannot address this being that our emotional empathy task did not distinguish between affective sharing and empathic concern in response to emotional images. However, our results from Study I suggest that the representation of affective sharing is valence-dependent, which is consistent with the involvement of simulation mechanisms and observation-experience neural matching in affective sharing.

Lastly, despite evidence presented here and elsewhere supporting the distinguishability of cognitive empathy, affective sharing, and empathic concern, it is important to note that these components of empathic responding can be elicited in response to similar situations and may not often occur in isolation. Indeed, recent work has demonstrated that the capacity to empathize cognitively and emotionally are independent at both a behavioural and neural level, but that they flexibly interact (Kanske, Bockler, Trautwein, Parianen Lesemann, & Singer, 2016). Accordingly, it is widely believed that these aspects influence one another and that both cognitive and emotional empathy contribute to our phenomenological experience of empathy (Cox et al., 2012; Decety & Svetlova, 2012; Kerem, Fishman, & Josselson, 2001; Shamay-Tsoory, 2011).

5.7 Limitations and Future Directions

The present work not only provides unique insight into the nature of empathic responding and its constituents, but it also highlights points of specific interest moving forward and remaining questions in the field. For example, Study I provided novel details concerning the cognitive and emotional empathy impairments in bvFTD, and Study II revealed an association between heightened coldhearted psychopathic traits and both reduced affective sharing and empathic concern. However, more work is needed to better understand the components affected in patient populations featuring empathy dysfunction, and whether these may be linked to simulation network deficits, with a view to informing targeted treatment or compensatory options for these devastating symptoms. Studies I and II also relied on a performance-based measure of empathic responding, the MET, which allows for the online assessment of empathy, but is also susceptible to response bias such as socially desirable responding. The addition of

physiological measures could be important for providing further insight into the nature of the affective response elicited in the future. Interestingly, in relation this to, results from our subjective arousal ratings in Study II suggested that there could be a disconnect between arousal generated in response to an emotional scene and empathic concern, but additional work including both behavioural and physiological measures is needed to elucidate this. The incorporation of indices to assess behavioural outcomes such as prosocial behaviour is also of interest, as though a link between empathic concern and prosocial behaviour has been fairly well-established (Batson, 1991; Eisenberg et al., 2006), the relationships between affective sharing, arousal, and prosocial responding remain fairly ambiguous. Of additional note, the emotional empathy task utilized in Study III did not distinguish between affective sharing and empathic concern, and instead used a metric that could capture both. Determining the involvement of the simulation network in cognitive versus emotional empathy was viewed as the natural first step for an initial quantitative comparison, being that these two facets are almost universally accepted, and have been well-established and dissociated. In addition, affective sharing and empathic concern are arguably more difficult to evoke independently. However, future work including indices tapping each of these facets is necessary to determine whether simulation mechanisms are particularly important for affective sharing, or empathic concern. Lastly, future investigations should also attempt to evaluate additional factors believed to influence empathic experience that have not been addressed presently, such as self-other distinction (Decety & Jackson, 2004; Singer & Lamm, 2009), emotion regulation and effortful control (Decety & Jackson, 2004; Eisenberg & Eggum-Wilkens, 2009), and similarity of the other to oneself (Hein, Silani, Preuschoff, Batson, & Singer, 2010; Krebs, 1975).

5.8 Conclusions

In conclusion, the results presented here advance our understanding of the nature of cognitive empathy, affective sharing, and empathic concern components of empathic responding, and how these aspects are differentially influenced in clinical and healthy populations. We uniquely identified differential deficits in these components in response to emotionally-charged social images in patients with bvFTD. In addition to providing evidence for the dissociability of

cognitive empathy, affective sharing, and empathic concern in a clinical model of empathy dysfunction, our results also suggested that valence may influence the representation of affective sharing for others' experiences, and patients with bvFTD may have a generalized deficit in affective responding to negative stimuli. Following this, the administration of the same task in a community sample revealed that coldhearted psychopathic traits disrupt affective sharing and empathic concern, whereas trait anxiety may influence subjective affective experience via generalized arousal with fewer implications for prosocial responding. Further evidence for the distinguishability of cognitive empathy, affective sharing, and empathic concern was also provided in the form of differential relationships between these components and subclinical psychopathic, autistic, and anxious traits. Lastly, we utilized separate fMRI localizers for cognitive empathy, emotional empathy, and the simulation network in healthy individuals, quantitatively demonstrating, for the first time, that action-perception simulation mechanisms are more involved in emotional than cognitive empathy. Thus, we also presented mechanistic evidence for the dissociability of cognitive and emotional facets of empathy. Taken together, these findings provide novel insight into the dissociability, influential variables, and neurocognitive mechanisms of cognitive empathy, and aspects of emotional empathy, including affective sharing and empathic concern. This highlights the complexity of empathic responding and the need to determine how these different constituents are affected in disorders featuring empathy impairments, with a view to identifying cognitive and neurological risk factors and providing targeted treatments for deficits in particular components of empathy.

5.9 References

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Appendices

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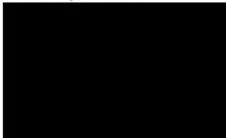
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Appendix C: Research ethics and approval number for Study I



Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Elizabeth Finger
Review Number: 17783
Review Level: Delegated
Approved Local Adult Participants: 24
Approved Local Minor Participants: 0
Protocol Title: A Phase I Dose Finding Study of Intranasal Oxytocin in Frontotemporal Dementia
Department & Institution: Clinical Neurological Sciences, London Health Sciences Centre
Sponsor: Alzheimer Society of Canada

Ethics Approval Date: April 21, 2011

Expiry Date: March 31, 2013

Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
UWO Protocol		
Letter of Information & Consent		2011/01/03
Caregiver Letter of Information & Consent		2011/01/03

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The UWO HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Signature

Ethics Officer to Contact for Further Information

<input checked="" type="checkbox"/> Janice Sutherland (jsutherland@uwo.ca)	<input type="checkbox"/> Elizabeth Wambolt (ewambolt@uwo.ca)	<input type="checkbox"/> Grace Kelly (grace.kelly@uwo.ca)
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Appendix D: Research ethics and approval number for Study II



Use of Human Participants - Ethics Approval Notice

Research Ethics

Principal Investigator: Dr. Derek Mitchell
 File Number:102711
 Review Level:Delegated
 Approved Local Adult Participants:200
 Approved Local Minor Participants:0
 Protocol Title:The impact of salient stimuli on the senses and behaviour
 Department & Institution:Schulich School of Medicine and Dentistry/Psychiatry,London Health Sciences Centre
 Sponsor:Natural Sciences and Engineering Research Council

Ethics Approval Date:November 07, 2012 Expiry Date:June 30, 2017

Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	Dr. A.J. Mao will be added to the study. A variant to the initially approved experiment has been added.	
Revised Letter of Information & Consent		2012/09/27

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/CH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 0000940.

Signature

Ethics Officer to Contact for Further Information

Janice Sutherland (jsutherf@uwo.ca)	Grace Kelly (grace.kelly@uwo.ca)	Shantel Walcott (swalcot@uwo.ca)
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Appendix E: Research ethics and approval number for Study III



Research Ethics

Western University Health Science Research Ethics Board HSREB Delegated Initial Approval Notice

Principal Investigator: Dr. Derek Mitchell
Department & Institution: Schulich School of Medicine and Dentistry/Psychiatry, Western University

HSREB File Number: 105764
Study Title: The neurocognitive correlates of distinct facets of empathy
Sponsor:

HSREB Initial Approval Date: December 16, 2014
HSREB Expiry Date: December 16, 2015

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Instruments	Autism Spectrum Quotient - Questionnaire Measure	
Instruments	State-Trait Anxiety Inventory - Questionnaire Measure	
Instruments	Interpersonal Reactivity Index - Questionnaire Measure	
Instruments	Empathy Quotient - Questionnaire Measure	
Instruments	Psychopathic Personality Inventory - Revised - Questionnaire Measure	
Instruments	Edinburgh Handedness Inventory - Questionnaire Measure	
Instruments	Instruments (Study Tasks)	2014/12/01
Recruitment Items	Flyer	2014/12/01
Recruitment Items	Phone Screen Script	2014/12/01
Western University Protocol		2014/12/09
Letter of Information & Consent		2014/12/09
Instruments	Phone Screen Questionnaire	2014/12/09

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review. If an Updated Approval Notice is required prior to the HSREB Expiry Date, the Principal Investigator is responsible for completing and submitting an HSREB Updated Approval Form in a timely fashion.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.


Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair

Ethics Officer to Contact for Further Information

Erika Basile ebasile@uwo.ca	Grace Kelly grace.kelly@uwo.ca	Mina Mekhail mmekhail@uwo.ca	Vikki Tran vikki.tran@uwo.ca
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Curriculum Vitae

Name: Lindsay D. Oliver

Post-secondary Education and Degrees:

University of Toronto
Toronto, Ontario, Canada
2006-2010 B.Sc. (Hons) with High Distinction

University of Edinburgh
Edinburgh, United Kingdom
2010-2011 M.Sc.

University of Western Ontario
London, Ontario, Canada
2012-2017 Ph.D.

Honours and Awards:

Harold Brett Memorial Fellowship in Neuroscience
University of Western Ontario
2016

Queen Elizabeth II Graduate Scholarship in Science and Technology
2015-2016, 2014-2015

Alzheimer Society London and Middlesex Doctoral Scholarship
2014-2016

Western Graduate Research Scholarship
2012-2016

Scotland Saltire Scholarship at the University of Edinburgh
2010

University of Toronto Isabel Warne Fellowship
2010

University of Toronto Dean's List
2007-2010

University of Toronto Howard Ferguson Scholarship
2006-2010

Queen Elizabeth II Aiming for the Top Scholarship

2006-2010

C.L. Burton Open Scholarship
University of Toronto
2009

Related Work Experience:

Teaching Assistant,
Introduction to Psychology (Psychology 1000)
University of Western Ontario
2013-2014

Teaching Assistant
Applications of Psychology (Psychology 2990)
University of Western Ontario
2012-2013

Publications:

Oliver, L. D., Vieira, J. B., Mitchell, D. G. V. (In Prep). The neurocognitive correlates of distinct facets of empathy: Greater involvement of simulation mechanisms in emotional relative to cognitive empathy.

Vieira, J. B., Wen, S., **Oliver, L. D.**, Mitchell, D. G. V. (Under Review). Enhanced awareness and “blindsight” for fear conditioned stimuli under Continuous Flash Suppression.

Oliver, L. D., Neufeld, R. W. J., Dziobek, I., & Mitchell, D. G. V. (2016). Distinguishing the relationship between different aspects of empathic responding as a function of psychopathic, autistic, and anxious traits. *Personality and Individual Differences*, *99*, 81-88.
doi: 10.1016/j.paid.2016.04.058

Oliver, L. D., Mitchell, D. G. V., Dziobek, I., MacKinley, J., Coleman, K., Rankin, K. P., & Finger, E. C. (2015). Parsing cognitive and emotional empathy deficits for negative and positive stimuli in frontotemporal dementia. *Neuropsychologia*, *67*, 14-26.
doi: 10.1016/j.neuropsychologia.2014.11.022

Finger, E. C., MacKinley, J., Blair, M., **Oliver, L. D.**, Jesso, S., Tartaglia, M. C., Borrie, M., Wells, J., Dziobek, I., Pasternak, S., Mitchell, D. G. V., Rankin, K. P., Kertesz, A., & Boxer, A. (2014). Oxytocin for frontotemporal dementia: A randomized dose-finding study of safety and tolerability. *Neurology*. doi: 10.1212/WNL.0000000000001133

Oliver, L. D., Mao, A., & Mitchell, D. G. V. (2014). “Blindsight” and subjective awareness of fearful faces: Inversion reverses the deficits in fear perception associated with core psychopathic traits. *Cognition & Emotion*, 1-22. doi: 10.1080/02699931.2014.976182

Oliver, L. D., Virani, K., Finger, E. C., & Mitchell, D. G. V. (2014). Is the emotion recognition deficit associated with frontotemporal dementia caused by selective inattention to diagnostic facial features? *Neuropsychologia*, *60*, 84-92. doi: 10.1016/j.neuropsychologia.2014.05.020