CHARACTERIZING EMPATHY IN AUTISM: EXPLICIT AND IMPLICIT PERSPECTIVES

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Para mi madre, todo lo bueno que hay en mí es de ti.
Para mi esposo, todo lo bueno en mí es gracias a ti.
Para Dios, todo el bien en mí es a través de Ti
Para mi familia cuyo amor inquebrantable me ancló e hizo todo esto posible
...
For my mother, all the good in me is *from* you
For my husband, all the good in me is *because* of you
For God, all the good in me is *through* You
For my family whose unwavering love anchored me and made this all possible.

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LIST OF ABBREVIATIONS

AFC Automated Facial Coding

AI Anterior Insula

AU Action Unit

BMA Bayesian Model Averaging

BOLD Blood Oxygen Level-Dependent

CE Cognitive Empathy

daMCC dorsal anterior mid-cingulate cortex

DAN Dorsal Attention Network

EE Emotional Empathy

EMFACS Emotional Facial Action Coding System

EMG Electromyography

FACS Facial Action Coding System

FC Functional Connectivity

fMRI Functional Magnetic Resonance Imaging

FSIQ Full Scale Intelligence Quotient

IAPS International Affective Picture System

IFG Inferior Frontal Gyrus

IPL Inferior Parietal Lobule

IRI Interpersonal Reactivity Index

IRI-EC Empathic Concern

IRI-FS Fantasy Scale

IRI-PD Personal Distress

IRI-PT Perspective Taking

MET The Multifaceted Empathy Test

MET-J MET-Juvenile

MNS Mirror Neuron System

mPFC medial PFC

NT Neurotypical

PFC PreFrontal Cortex

PIQ Performance Intelligence Quotient

SCR Skin Conductance Response

SRS-2 Social Responsiveness Scale-2

ToM	Theory of Mind
TPJ	Temporo-Parietal Junction
VIQ	Verbal Intelligence Quotient
WASI-II	Wechsler Abbreviated Scale of Intelligence Second Edition
WSS	Within Sum of Squares
QMEE	Questionnaire Measure of Emotional Empathy

CHAPTER 1

Introduction

1.1 Preface

The following sections are intended to provide the reader with a snapshot of the key elements involved in the present investigation as well as a foundation from which to critically assess the originality and impact of the present research. The introduction begins with a general overview of empathy and its importance for social function. A brief history of empathy research is provided next, highlighting how challenging it has been to capture the inherent complexities of the empathic experience involving both brain and behavioral responses measured using implicit and explicit tools. Special attention is placed in the history section on some of the most consequential studies on empathy to provide the reader with a proper sense of the limitations that informed current research procedures. The neural underpinnings of empathy are explored next, followed by a summary of empathy research in autistic populations. The notion of autism being an empathy condition is challenged against the backdrop of a growing body of literature suggesting otherwise. Finally, the unifying rationale and objectives for the thesis are introduced. While this chapter is not designed to be a comprehensive review, more detail, background, and rationale for each component of the investigation are provided in the respective chapters to come.

1.2 The Human Experience of Empathy

The social and conspecific-reliant nature of humanity has long been the subject of intrigue and research. The ability to appropriately navigate complex social environments and interactions requires distinct but related cognitive and emotional capabilities. Prosocial behaviors like cooperation, kindness, and collaboration amongst social partners are essential for human survival and prosperity (Howe, 2012; Carter et al., 2011). Intended to promote social good standing, these positive and helpful behaviors are thought to arise from important foundational antecedent empathic skills (Eisenberg and Miller, 1987; Eisenberg et al., 2005). While many species demonstrate cooperative and collaborative behaviors, our enhanced capacity to engage in verbal and nonverbal forms of empathy, to read and express internal emotional states, and to act upon these separate but related information streams is thought to be a core feature of what makes us human (Howe, 2012).

1.3 History of Empathy Research

Contemporary empathy research dates back to the 1940s, when the construct was empirically quantified through descriptive and experimental approaches (Gladstein, 1984; Neumann et al., 2015). This early period also marks the origin of a wide variation in empathy definitions that were influenced by the respective fields (i.e., social, psychology, development) assessing this phenomenon. Each discipline, with their own perspectives, developed field-specific measures to quantify what is otherwise an abstract and subtle social experience. This lack of precision in definition led to opposing views on how to study, interpret, and report empirical findings. While there is some consensus emerging from more recent studies, significant advancements are still hampered by the lasting influence of unclear definitions (Hall and Schwartz, 2019). This section will cover some of the more historically relevant opposing views and findings by introducing and highlighting methods and approaches employed in early psychology, social, and neuroscience research.

1.3.1 Unidimensional Approaches

Since its inception as a research topic, separate views on how to define empathy gave way to two tracks of method development. One track focused on the more cognitive aspects of empathy like the ability to mentally take on the perspective of someone other than yourself, while the other focused more on the vicarious affective experience of witnessing another person's feelings and emotional states. Several popular measures ensued from cognitive, and to a lesser extent, affective takes on empathy including Dymond's scale for empathic ability (Dymond, 1949), and the Questionnaire Measure of Emotional Empathy (QMEE; Mehrabian and Epstein (1972), respectively. These are further discussed as exemplars of the state of empathy research in the mid-20th century and the path from these early contributions to current methods.

1.3.1.1 Dymond's Empathic Ability Scale

The Empathy Ability Scale (Dymond, 1949) characterized empathy as the projection of an internal representation of the self onto another person's thoughts, feelings, and actions in an effort to understand that person's experiences. To measure this, participants used a five-point scale to rate themselves and one other participant on six personal traits (i.e., friendly/unfriendly, secure/insecure, and follower/leader) after a brief period of getting to know each other. Participants were also asked to rate themselves as they believed the other participant would rate them and finally, to rate the other participant as they would rate themselves on the same six personal traits. Empathy scores were calculated as the total points that prediction ratings of others deviated from their actual self ratings such that higher scores indicated lower empathy (i.e., my empathy score = other people's self ratings - my prediction ratings of them). Although it was a promising direction and one of the first of its kind, the Empathy Ability scale was found to exhibit questionable validity and to be subject to social and cultural biases (Lindgren and Robinson, 1953).

Social and/or cultural desirability bias occurs when there is a consistent uneven distribution of self-report ratings that favor desirable traits. On separate assessments, Dymond's Empathic Ability Scale exhibited an uneven distribution of ratings on their 5-point scale for questions like “How friendly or unfriendly do you think you are to him or her?” that favored higher scores like “4- fairly friendly” and made it unclear whether answers were based on true empathic abilities or culturally/socially reinforced concepts of how they should feel and act. The inclination to answer survey questions based on socially desirable and favorable traits varies with social and cultural norms that serve as a baseline for what answers place the respondent in a favorable position (Nederhof, 1985).

1.3.1.2 Mehrabian and Epstein’s Questionnaire Measure of Emotional Empathy

Separate from the cognitive role-taking and inference view of empathy, the vicarious and somewhat abstract emotional facet of empathy was also difficult to measure using self-report and physiological tools available in the latter half of the 20th century. Early paper and pen emotional empathy questionnaires were also subject to social desirability biases while physiological metrics were yet too premature for reliable comparative use.

In an effort to correct for social biases inherent to popular personality assessments of the time, Mehrabian and Epstein developed the Questionnaire Measure of Emotional Empathy (QMEE), a questionnaire structured to assess various aspects of emotional empathy like emotional contagion and sympathetic tendency (Mehrabian and Epstein, 1972). Items in the final measure included 33 statements like “I like to watch people open presents” and “When a friend starts to talk about his problems, I try to steer the conversation to something else”. The softer verbiage of these items captures affective empathy responses (e.g., how they would respond) without explicitly asking participants what their empathic response is (e.g., ‘I am sympathetic to my friend’s problems’, see Table 1.1 for a full list of items). For each statement, participants were asked to rate their degree of agreement using a Likert-like scale ranging from “very strong agreement” to “very strong disagreement”. The survey’s validity was assessed by administration in two separate contexts that invoke emotional empathy: 1) aggression and 2) helping behaviors (Mehrabian and Epstein, 1972).

Aggression experiments followed Buss’s teacher-student format (Buss, 1961). Briefly, participants were made to believe that they had been assigned the teacher role at random and would present a ’student’ with a series of questions. The student role was played by a confederate who was part of the research team). Participants were instructed to reinforce ‘students’ for correct answers or administer a shock for incorrect answer responses that were pre-determined by the researcher. Confederate-students were either in the same room as the participant or in an adjacent room and were never really shocked but trained to act as if they had been. For their experiment testing the effects of empathic tendency on helping behaviors, Mehrabian and Epstein paired college-age participants with seemingly distraught confederates in a waiting room. Confederates were trained to present a volunteer opportunity for participants under the guise that their volunteered time would help confederates execute their own psychology experiment in order to pass their course.

In their aggression experiments, Mehrabian and Epstein found that participants with higher scores on the QMEE were less likely to punish confederates for their wrong answers if the confederate was sitting in the same room with them. Conversely, those who scored lower on their empathy measure were shocking confederates at comparable rates irrespective of whether the person was in the same room with them or in an adjacent room where they could be heard but not seen. It is worth noting that experiments using the student-teacher format as described by Buss (1961) are now considered unethical, given the use of deception and the potential for the belief that one is administering shocks to cause significant psychological distress (Miller, 2009).

In their helping experimental scheme, participants were asked to complete a series of personality assessments designed to capture traits like emotional dependence and approval seeking tendencies in addition to the QMEE. Participants' characteristic emotional states were also assessed using the Mehrabian and Russell (1974) three independent scale model (e.g., pleasure, arousal, and dominance). After about 20 minutes, experimenters paused the personality assessments to inform participants that they would listen to music in a separate room with another person (a confederate), report their own reactions to the music, and predict each other's reactions. After 5 minutes, both the participant and confederate were moved into a 'waiting room' for an additional 3-minute period during which the confederate was instructed to make a plea for help. The tendency to help was measured as the amount of time participants were willing to volunteer in half hour increments. The authors found that empathic tendency significantly predicted helping tendency and suggested that empathic people are receptive to the needs of their peers and colleagues.

Towards the goal of developing a reliable measure, Mehrabian and Epstein used a more dimensional approach and carefully worded question items against social desirability bias (Table 1.1). However, the authors may have inadvertently introduced a different type of bias, consistency bias, by having participants complete the personality assessments and commitments to help on the same day. It is possible that answering questions about empathic ability may have influenced participants to behave in a manner that was more consistent with their responses and not with how they really felt in the moment or would behave under more general circumstances. Nevertheless, their main findings suggested that there is a direct correlation between empathic tendency and emotional arousal (as measured by Mehrabian and Russell's three factor theory of emotion) whereby higher empathy individuals tend to be more emotionally aroused to the positive and negative experiences of others. The utility of the QMEE was supported by this finding, underscoring its utility in both positive and negative contexts. This initiative to identify and quantify the relation between empathy and arousal further emphasized the inherent multidimensional nature of empathy.

1.3.2 Multidimensional & Multimodal Approaches

Early self-report empathy measures not only struggled with items that were confounded by social norms but also with conflicting definitions and perspectives on how to operationalize and measure empathy. While unidimensional measures provided significant insights, later studies began exploring separate facets of cognitive and emotional empathy, considering the interplay between sympathy (a general concern for others) and motivation towards prosocial behaviors (a product of empathy) in their research designs. For example, Coke et al. (1978) suggested that taking on the perspective of others (i.e., someone in need) engenders emotional empathy which in turn produces helping behaviors. They proposed a two-stage model involving both a cognitive appraisal of the physiological arousal induced by observing someone in need of help and an emotional response salient enough to trigger the motivation for prosocial behavior.

By 1980, this new framework for a more integrated multidimensional conceptualization of empathy was gaining ground (Hogan, 1969; Feshbach, 1975; Coke et al., 1978). The work of Davis (1980, 1983) in developing the Interpersonal Reactivity Index (IRI) was instrumental in promoting this shift toward multidimensionality. The IRI was among the first well validated measures designed to tap into several separate but related components of empathy and is currently among the most cited empathy measurements. The survey includes four 7-item subscales (Perspective Taking (IRI-PT), Fantasy (IRI-FS), Empathic Concern (IRI-EC), Personal Distress (IRI-PD), each with its own score thus allowing for the assessment of how each component influences empathic behavior. Davis (1980) structured the PT subscale to gauge participants' inclination to spontaneously adopt other people's point of view, the FS to tap into respondents' tendencies to transpose themselves imaginatively into the feelings and actions of fictitious characters in books, movies, and plays, the EC subscale to measure "other-oriented" feelings of sympathy and concern for unfortunate others, and the PD subscale to assess "self-oriented" feelings of anxiety and uneasiness in tense interpersonal contexts.

The success of the IRI can be largely attributed to its four-subscale design. This dimensional feature has been exploited by empirical empathy studies based on the definitions and constructs of empathy of interest. Studies adopting a multidimensional definition have combined the four scales to derive a total empathy score, while others chose subscales based on specific subconstructs of interest (Wang et al., 2020). This flexible adaption of the IRI has maximized its utility across various disciplines, making it the most common measure in empathy research (Wang et al., 2020). The IRI has been reported to have good concurrent and convergent validity in a large sample of American college students (Davis, 1983) but also been adapted and validated across several languages like Spanish (Lucas-Molina et al., 2017; Garcia-Barrera et al., 2016) and French (Gilet et al., 2013). Popular as it may be, however, the IRI is not without limitations.

Self-report questionnaires like the IRI are often subject to limited ecological validity. Limited ecological validity occurs when the results from assessments, often administered in controlled settings, are not transferable to real life situations. Further, self-report measures require people to think in hypotheticals making them more likely to tap into what might happen in an ideal context rather than a more representative or real-time situation. This inherent abstract thinking required by these questionnaires also limits their utility in clinical populations that struggle with this level of self-reflection, such as autism.

To circumvent this and aforementioned challenges, self-report measures are now frequently accompanied by performance and behavior tasks that offer more objective metrics than self-impressions (Dunning et al., 2003; Brackett et al., 2006; Donaldson et al., 2022). Performance and behavior tasks include discrete skill or ability assessments (e.g., emotion recognition) and physiological measures (e.g., functional brain networks), respectively. Together they provide unique insights about people's lived experiences from explicit and implicit perspectives that may or may not always converge. For example, a person may report that an emotionally charged image depicting someone in pain has no effect on them (explicit), but an elevated heart rate (implicit) might suggest otherwise.

Use of the well-validated International Affective Picture System (IAPS) repository of emotionally charged images as stimuli has been a popular approach to tap into empathy and related constructs (Bradley and Lang, 2007; de Sousa et al., 2010). The IAPS provides a normative set of emotionally charged images for use in experimental research (Lang et al., 1997). The Multifaceted Empathy Test (MET) for example, used IAPS photos showing people in realistic emotionally charged situations to tap into cognitive and emotional empathy simultaneously (Dziobek et al., 2008). The MET asseses emotional empathy by asking participants to rate their level of emotional relatedness to the person in the picture, and cognitive empathy by asking participants to label the emotion of the person in the picture (Dziobek et al., 2008). A third measure quantifies arousal by asking participants to rate how excited the images make them feel. The MET is a well validated computer task that has now been used for indexing emotional and cognitive components of empathy in clinical conditions like autism (Dziobek et al., 2008; Poustka et al., 2010; Mazza et al., 2014), psychopathy (Foell et al., 2018), and broader clinical conditions (Irorutola et al., 2020). Validation was assessed against the long-standing standard survey of empathy: Dziobek et al. (2008) reported that the MET's emotional and cognitive sub scales are well correlated with corresponding IRI subscales like IRI-PD and IRI-PT, respectively. In Chapter 2, I use the MET to extend previous autism findings by using the MET in a single large cohort of broad age range and test for age, sex, and valence effects.

The MET task described above constitutes explicit measures of empathy, and its measure of emotional empathy may be susceptible to many of the same biases as self-report questionnaires. Implicit methods that are less susceptible to social biases include reflexive facial expressions (Sonnby–Borgström, 2002; Drimalla et al., 2019) and autonomic physiological responses like the skin conductance response (SCR; Levenson and

Ruef 1992) . The SCR serves as an index of transient autonomic activity, while reflexive facial expressions provide behavioral compliments to emotion recognition. These separate channels of empathy responses have seldom been investigated simultaneously using a single task. Drimalla et al. (2019) is among such few studies with their investigation on the contribution of facial mimicry (i.e., facial expressions matching the expression of another person) to cognitive and emotional empathy using the MET. The authors reported positive associations between inter-individual differences in emotional and cognitive empathy and degree of facial mimicry (Drimalla et al., 2019). Facial mimicry has been measured using electromyography (EMG), manual behavioral coding systems such as Paul Ekman's Facial Action Coding System (FACS; Ekman and Friesen 1978a; Ekman et al. 2002), and more recently, using automated facial coding (AFC) algorithms built on the FACS system. In Chapter 3, I use AFC to interrogate spontaneous facial expression production, an implicit proxy for empathy, in response to emotionally charged images of human facial expression. Notably, all the methods covered so far came about from the influence and at the mercy of advancements and maturation of social-cognitive psychology as a discipline. The development and advancement of neuroscientific methods like functional magnetic resonance imaging (fMRI) made it possible to gain important insights on the circuits involved in empathy. fMRI tools offer another implicit way to measure physiological activity and identify behavioral brain markers that are less susceptible to social biases. Important and relevant findings regarding the neural basis of empathy are discussed in the following section.

1.4 Neural Basis of Empathy

Many human brain imaging studies suggest that observing the emotional states of others recruits brain networks involved in the firsthand experience of those same emotions (Preston and de Waal, 2002; Keysers et al., 2004; de Vignemont and Singer, 2006). Specifically, a collective of neuroimaging empathy studies have consistently identified task-specific blood oxygen level-dependent (BOLD) response in several emotional and cognitive specific brain regions including the anterior insula (AI; Singer et al. 2004), dorsal anterior mid-cingulate cortex (daMCC; Fan et al. 2013), inferior frontal gyrus (IFG; Nummenmaa et al. 2008), temporo-parietal junction (TPJ; Frith and Frith 2001), prefrontal cortex (PFC; Schulte-Rüther et al. 2010; Amodio and Frith 2006), and to a lesser extent, somatosensory cortices (Keysers et al., 2004). The importance of these regions for empathy constructs is further supported by findings that trauma-based injuries to these areas can induce sudden emotional and cognitive social impairments (Rowe et al., 2001; Channon and Crawford, 2010). The respective contributions of each of these regions to emotional and cognitive empathy are summarized in the following sections.

1.4.1 Neural Basis of Cognitive Empathy

Cognitive empathy involves the ability to mentalize and understand another person's perspectives and intentions. Theory of mind (ToM), one aspect of cognitive empathy, involves the ability to go beyond mentalizing and extract information from observing others to predict behavior (Shamay-Tsoory, 2011; Amodio and Frith, 2006). Much of what we know about the neural underpinnings of cognitive empathy comes from task-based fMRI studies using ToM tasks–largely due to the popularity of the theory's relationship with social cognition in a variety of psychopathologies. In their review of 40 separate ToM neuroimaging studies, Carrington and Bailey (2009) found that 37 reported recruitment of the medial PFC (mPFC), and that 23 of the 40 reported recruitment of the TPJ. A separate meta-analysis suggests that the TPJ is important for making rudimentary inferences about the intentions and perspectives of others and discriminating them from intentions and perspectives of the self, while the mPFC is important for higher level inferences that recruit emotional and memory inputs towards making sound behavioral decisions (Van Overwalle, 2009). To better understand how these regions are involved in social interactions, imagine you are walking into your favorite store for some light shopping. As you approach the door you notice that someone is holding the door open, and as you get closer you realize that they are holding the door open for you. Flushed with gratitude, you begin to walk a little faster- you don't want to appear rude. The motor behavior (door held open) is assessed by the TPJ for its social context and intention (the door is being held open for you). Information from this appraisal is sent to the mPFC where it is further evaluated, and you conclude that this act of kindness should not be repaid with rudeness so a signal is sent to motor and expressive language cortices for you to speed up to meet the stranger and thank him. Thus, through the mPFC's high degree of connectivity to the TPJ and other socially relevant regions, these separate but related functions work together to inform our preferences and behavior in social situations that require empathic responses.

1.4.2 Emotional Empathy

A common and everyday example of emotional empathy is emotional contagion- a phenomenon in which someone's feelings and associated reactions are reflected as similar feelings and behaviors in others. Emotional contagion is a basic building block for human interaction that makes it possible to understand human cognition, emotion, and behavior (Hatfield et al., 2011). The ability to understand the actions of others is crucial for social organization, survival, and learning through imitation- a skill that is particularly well developed in humans (Rizzolatti et al., 2001, 2009). The simulation theory posits that emotional contagion is achieved by recruitment of neural ensembles during observations of others that match the neural ensembles recruited by similar situations occurring in the self (Gallese, 2007). This line of thought was further supported by the discovery of mirror neurons in the ventral premotor and parietal cortex of non-human primates that fired both when monkeys performed an action and when they watched another monkey perform the same action (Rizzolatti and Craighero, 2004; Rizzolatti et al., 2009). This pattern suggests that the corresponding putative human mirror neuron system (MNS) (Rizzolatti et al., 2009) may be the mechanism subserving empathy constructs like motor empathy (yawns), and emotional contagion.

In humans, the putative MNS comprises the IFG and the inferior parietal lobule (IPL) (Shamay-Tsoory, 2011). Both the IFG and IPL are part of a network of brain areas that are engaged during externally directed tasks, the dorsal attention network (DAN). The IFG has been particularly implicated as the neural basis for emotional empathy and related constructs like emotional contagion, emotion recognition, and understanding (Schulte-Rüther et al., 2007; Nummenmaa et al., 2008; Niedenthal, 2007). For example, mirror neurons that respond to facial expressions in the IFG are thought to mediate the production of facial expressions that mimic the observed facial expressions of others (Keysers and Gazzola, 2006). Recruitment of the IPL is also important for identifying the motor intentions of others, information which is then projected to the TPJ for further social evaluation (Van Overwalle, 2009).

Emotional empathy has also been linked to connectivity between the orbital, cingulate, and insular cortices (Jabbi and Keysers, 2008; Decety et al., 2010; Uribe et al., 2019) The AI and dorsal anterior cingulate cortex (dACC) are part of the salience network, responsible for assessing sensory input for affective importance and relevance. The anterior insula (AI) has been further implicated in regulating the neural integration from the emotional, cognitive, and sensorimotor information streams important for the experience of empathy (Menon and Uddin, 2010; Mutschler et al., 2013). A proposed mechanism for this involves the bidirectional connectivity between anterior and posterior insula to modulate autonomic responses to salient stimuli and functional coupling with the anterior cingulate cortex (ACC) that in turn facilitates quick access to motor systems like the DAN (Menon and Uddin, 2010; Uddin, 2015).

1.5 Brief Summary of Empathy Research in Autism

The literature reviewed thus far comes from studies on neurotypical (NT) healthy populations but links between empathy and autism date back to the first published clinical account of the autistic profile (Kanner, 1943). In this seminal paper, Leo Kanner described autism as an affective or emotional condition in which children preferred to play alone and lacked the ability to establish social relations with others. Autism is characterized by challenges with social communication, repetitive behaviors, and atypical responses to sensory input, with an onset in the early developmental period (American-Psychiatric-Association, 2013). Autism's current prevalence rate is 1 in 44 American 8-year-old children (Baio et al., 2018). It is four times more common in boys than girls (though see Krahn and Fenton 2012; Dworzynski et al. 2012), and is reported across all racial, ethnic, and socioeconomic groups (Baio et al., 2018). Within the social domain, significant challenges with social interactions like developing and maintaining friendships, and social cognition are hallmark features of autism (Jobe and Williams White, 2007; Schulte-Rüther et al., 2010).

Several theories have been proposed to explain the social, cognitive, and emotional symptoms observed in autism. Among these, Baron-Cohen et al. (1985) proposed that a 'cognitive deficit' could explain pervasive social impairments in autism. Specifically, the authors suggested that ToM capabilities like mentalizing and ascribing beliefs to others were impaired in autism, contributing to social deficits. Separately, the broken mirror hypothesis (MNS dysfunction), has been suggested to explain dampened emotional empathy responses in autism (Dapretto et al., 2006). A brief overview of the historical highlights of empathy research in autism is provided here but is further discussed in chapters to come.

1.5.1 Cognitive Empathy in Autism

Cognitive empathy (CE), the ability to understand and make inferences from the perspectives of others, studies in autism have used both self-report and performance-based tasks of social cognition. Studies using tasks like the MET have explored cognitive empathy constructs like emotion recognition (Dziobek et al., 2008; Mazza et al., 2014). Difficulties with recognition of emotional facial expressions have long been documented in autism (Hobson, 1986) and even explored as potential biomarkers (Loth et al., 2018). Dziobek et al. (2008) found that when looking at emotionally charged images, emotion labeling accuracy (cognitive empathy) was significantly lower in high functioning autistic adults compared to neurotypical counterparts. Mazza et al. (2014) sought to extend these findings by assessing the effect of emotional valence on empathy using the MET in autistic adolescents. The authors reported comparably low emotion recognition accuracy to both positive and negative images. Together, these studies strongly support a global impairment of cognitive empathy in autistic adolescents and adults. In Chapter 2, we replicate and extend these results to show that there is a global age group effect on emotion recognition accuracy on the MET.

Functional connectivity studies have also suggested that dysfunctional brain networks may be responsible for empathy challenges in autism. For example, reduced vmPFC recruitment in autism during an emotion recognition task highlights the importance of this region for processing cognitive components of empathy (Klapwijk et al., 2016; Schulte-Rüther et al., 2010). These results are further corroborated by findings of reduced hemodynamic responses in the medial prefrontal cortex of young autistic adults in response to emotionally charged stimuli depicting someone intentionally hurting another person compared to matched controls (Fan et al., 2013; Lassalle et al., 2018).

1.5.2 Emotional Empathy in Autism

Unlike cognitive empathy research in autism, emotional empathy studies have been largely inconclusive. Self-report studies have primarily relied on the IRI and concluded that autistic populations do not score significantly lower than NTs in the empathic concern subscale but instead score higher in the personal distress subscale (Rogers et al., 2007; Dziobek et al., 2008). Computer tasks like the MET corroborate this finding when considering emotional empathy as a whole (Dziobek et al., 2008; Poustka et al., 2010) but reveal dampened emotional resonance to negative images (Mazza et al., 2014).

In contrast to these predominantly null findings, other studies do report reduced emotional empathy on the IRI, and in response to distressing videos in autism compared to NT controls (Trimmer et al., 2017). Trimmer et al. (2017) noted paradoxically intact physiological arousal responses in autism, however. The authors interpret these results as suggestive of a disconnect between what is felt (physiological response) and the interpretation of arousal in autism. Separate studies of spontaneous facial expression production in autism have found similar patterns of altered skin conductance responses but normal facial EMG responses to emotionally salient stimuli (Mathersul et al., 2013a) that are as strong for positive stimuli as they are for negative stimuli (Rozga et al., 2013).

These discrepancies may be due in part to methodological differences like different sources and type (image or video) of emotionally charged stimuli or differences in sample characteristics. Nevertheless, having a clear understanding of the contribution of emotional empathy to the greater empathy phenotype in autism warrants further investigation.

1.6 Summary and Objectives

Much of the groundwork for elucidating the multidimensional nature of empathy in autism had been laid out at the beginning of this dissertation project. It was clear that separate but related lines of work were challenged by small sample sizes, empathy definitions that were not always in agreement, and varied methodologies. Further, the importance of the matter at hand was becoming increasingly apparent as rising prevalence rates underscored the urgency for the development and validation of efficacious socio-behavioral interventions. While most cognitive empathy assessments suggested a decreased capacity for emotion recognition, understanding, and attribution, it was unclear whether this was a global effect or specific to context, age, and emotional valence. Similarly, inconclusive emotional empathy findings incorporated both psychological and physiological assessments in different experimental contexts making it difficult to draw firm conclusions. Thus, the goal of this project was to address some of these limitations by investigating multiple channels of empathy across a single sample of wide age range using the same task.

The following chapters are the culmination of this effort and address the multiplicity of empathy at the levels of both brain and behavior in individuals with and without autism. The first objective was to investigate self-reported levels of emotional and cognitive empathy in the context of positive and negative emotionally charged images using the well-validated MET (Chapter 2). The second objective was to investigate differences in spontaneous facial expression production while completing the MET (Chapter 3), using automated facial action coding. This was accomplished under the theoretical framework that facial expression production is inherently variable and that failure to limit inter-individual variability can lead to obscured group differences. Lastly, the investigation bridges brain and behavior by investigating resting connectivity between brain regions implicated in empathy (Fig 1.1) and their relation to empathy scores on the MET (Chapter 4). The final chapter summarizes and proposes a unified interpretation of the empathic experience in autism using collective insights from the present studies.

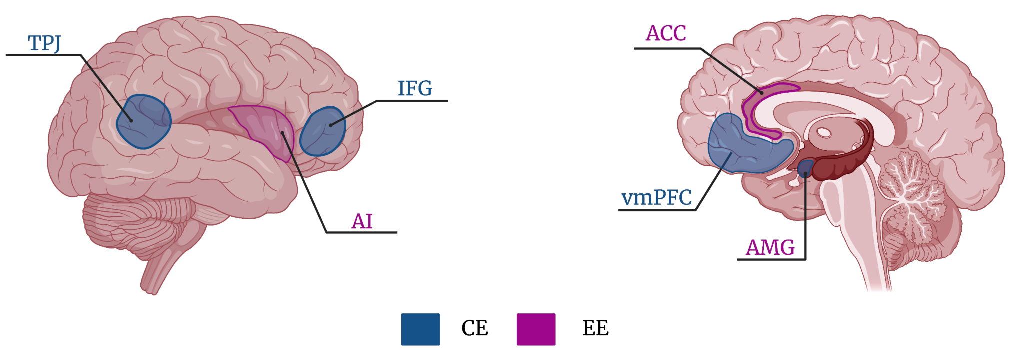

Figure 1.1: Cognitive Empathy Network

Cognitive Empathy: TemporoParietal Junction (TPJ);Inferior Frontal Gyrus (IFG);ventromedial PreFrontal Cortex (vmPFC)
Emotional Empathy: Anterior Insula (AI);Anterior Cingulate Cortex (ACC);Amygdala (AMG)

Table 1.1: Items on Mehrabian and Epstein's Questionnaire Measure of Emotional Empathy

1	It makes me sad to see a lonely stranger in a group
2	People make too much of the feelings and sensitivity of animals
3	I often find public displays of affection annoying
4	I am annoyed by unhappy people who are just sorry for themselves
5	I become nervous if others around me seem to be nervous
6	I find it silly for people to cry out of happiness
7	I tend to get emotionally involved with a friend's problems
8	Sometimes the words of a love song can move me deeply
9	I tend to lose control when I am bringing bad news to people
10	The people around me hove a great influence on my moods
11	Most foreigners I have met seemed cool and unemotional
12	I would rather be a social worker than work in a job training center
13	I don't get upset just because a friend is acting upset
14	I like to watch people open presents
15	Lonely people are probably unfriendly
16	Seeing people cry upsets me
17	Some songs make me happy
18	I really get involved with the feelings of the characters in a novel
19	I get very angry when I see someone being ill-treated
20	I am able to remain calm even though those around me worry
21	When a friend starts to talk about his problems, I try to steer the conversation to something else
22	Another's laughter is not catching for me
23	Sometimes at the movies I am amused by the amount of crying and sniffling around me
24	I am able to make decisions without being influenced by people's feelings
25	I cannot continue to feel ok if people around me are depressed
26	It is hard for me to see how some things upset people so much
27	I am very upset when I see an animal in pain
28	Becoming moved in books or movies is a little silly
29	It upsets me to see helpless old people
30	I become more irritated than sympathetic when I see someone's tears
31	I become very involved when I watch a movie
32	I often find that I can remain cool in spite of the excitement around me
33	Little children sometimes cry for no apparent reason

CHAPTER 2

Multifaceted empathy differences in children and adults with autism[1]

2.1 Introduction

Considered a social 'glue' that allows for successful human relationships, empathy is an essential component of social interactions with which individuals on the autism spectrum reportedly struggle (Baron-Cohen and Wheelwright, 2004; Harmsen, 2019; Song et al., 2019b). Various studies investigating empathy differences in autism have reported conflicting results, including intact empathic physiological responses (Blair, 1999; Trimmer et al., 2017) but reduced or dampened self-reported empathy (Baron-Cohen and Wheelwright, 2004; Trimmer et al., 2017). Notably, empathy research has been slow to develop a clear, operationalized definition of "empathy" or its various components, and there remains no global consensus on best practices for the measurement of this construct (Frankel, 2017; Preston and de Waal, 2002). Thus, early autism studies employing different approaches to measure this inherently complex neuropsychological concept often reported findings based on disparate empathy subconstructs (Song et al., 2019b; Cox et al., 2012; Fletcher-Watson and Bird, 2020).

Empathy has traditionally been considered to include the distinct constructs of **emotional empathy**, the ability to *share* another person's feelings, and **cognitive empathy**, the capacity to *understand* such feelings (Cox et al., 2012; Shamay-Tsoory et al., 2009). A third, now increasingly differentiated component, **empathic concern**, has recently gained consideration as part of the multifaceted nature of empathy (Jordan et al., 2016; Zhao et al., 2019; Zickfeld et al., 2017). Empathic concern is characterized by greater *others*-oriented relational mentalities and encompasses emotional sentiments (e.g., sympathy and compassion) towards someone else's experience. Though the distinction between emotional empathy and empathic concern is subtle, emotional empathy describes *sharing* another's feelings, which involves self-orientation (i.e., "mirroring" emotion), while empathic concern does not require having the same feeling but being aware of and concerned about another's feeling. This capacity for *self*-other distinction is considered to be crucial and integral to the empathic experience (Håkansson Eklund and Summer Meranius, 2020).

Many studies have now explored these three constructs both separately, and to a lesser extent, in some combination within a single autism sample. This is notable given the growing evidence that these processes typically work together to form a unified percept (Håkansson Eklund and Summer Meranius, 2020). Thus, it would be difficult, for example, to speculate on the underpinnings of emotional empathy differences and how

[1]Parts of this chapter have been adapted from "Multifaceted Empathy Differences in Children and Adults with Autism", published in *Scientific Reports* and has been reproduced with the permission of the publisher

these may relate to autism features, without assessing these separate but related constructs simultaneously. To this end, empathy differences between autistic and neurotypical (NT) individuals have been primarily assessed using multidimensional self-report tools like the Interpersonal Reactivity Index (IRI; Lang et al. 1997), Empathy Quotient (EQ; Baron-Cohen and Wheelwright 2004), and Questionnaire of Cognitive and Affective Empathy (QCAE; Reniers et al. 2011; see Song et al. 2019b for a review). While these well-validated self-report measures have informative potential, they are not without limitations. Primarily, they are subject to social desirability biases and subjective variability in interpretation that can ultimately result in under- or over-reporting (Dziobek et al., 2008).

To address the limitations of widely-used self-report measures, Dziobek and colleagues (2008) developed the Multifaceted Empathy Test (MET) as a performance-based measure of empathy. The MET is a computerized task that assesses both emotional and cognitive empathy in response to a series of emotionally charged facial expressions. This task was designed to be more ecologically valid than self-report measures of empathy, in that it does not rely as heavily on the level of insight an individual has into their own emotions. The MET was also designed to mitigate potential social desirability biases in empathy ratings by asking participants to rate their level of arousal in response to each stimulus, which ostensibly serves as an implicit measure of emotional empathy. This measure has contributed meaningfully to the study of empathy in autism, as large effects of diagnosis on the cognitive empathy (i.e., emotion recognition) subcomponent of the MET (Dziobek et al., 2008; Mazza et al., 2014; Poustka et al., 2010) indicate that group differences in empathy demonstrated using questionnaire measures are not simply due to differences in emotional self-awareness or social desirability biases.

The ability to distinguish positive from negative emotional situations is an important feature of empathy and drives our tendency to engage in prosocial behaviors. This important skill underlies our ability to produce appropriate resonant behaviors that ultimately help build social rapport (Luberto et al., 2018). Although some prior work suggests that emotional valence may moderate diagnostic group differences in empathy (Mazza et al., 2014; Luberto et al., 2018), studies on this topic are scarce and inconsistent, and it remains unclear whether these differences relate to autism symptomatology.

2.2 The Present Study

In light of this emerging but incomplete picture of empathy in autism, the present study explores empathy as a multifaceted construct that is potentially modulated by valence in individuals with autism. To extend previous findings, an age-appropriate adapted version of the MET, the MET-Juvenile (Poustka et al., 2010), consisting of 16 positive and 16 negative emotional images (decreasing testing time to accommodate younger participants), was administered to a large sample with a wide age range. Notably, though age effects for specific components of empathy have been reported (Peterson, 2014; Schulte-Rüther et al., 2014), there is no clear agreement on how these capacities may be related to maturation (Song et al., 2019b). For example, while some studies suggest that empathy increases with age (Peterson, 2014), others suggest that older adults have lower empathic abilities (Phillips et al. 2002; see Sun et al. 2018 for a review). Thus, participants from a broad age range were included in the present study thereby ensuring grounds for exploration of age effects. Group differences in cognitive and emotional empathy (including empathic concern), were assessed globally in the context of the hypothesis that empathy is a complex, developmental process involving emotional and cognitive components that are moderated by stimulus valence.

2.3 Methods

2.3.1 Participants

Participants in this study were recruited from the community through posters and social media postings as well as from a pool of participants in previous larger and longitudinal lab studies who consented to be re-contacted. During the recruitment period, our stance on study design for case-control comparisons has evolved; early in this period, the goal was to achieve a "clean" autism sample and thus excluded most co-occurring psychiatric and developmental conditions within the autism group. As time has gone by, we have seen that these samples are not representative of the population and have opted to be more inclusive and attempt to control for co-occurring conditions in both groups analytically instead, though we have been slower to adopt this for control groups. Thus, this sample represents a blend as our approach has evolved.

Co-occurring mental health symptoms in our autism group were screened for using the Achenbach System of Empirically Based Assessment (ASEBA) School Age (6–18) & Adult (18–59) forms. Overall, we collected ASEBA data on 90/184 participants (24 Autism, 66 NT). Of these, 11 Autism participants endorsed clinically significant symptoms of depression, 8 endorsed clinically significant symptoms of anxiety, and 9 endorsed clinically significant symptoms of ADHD. Of the 66 NT participants with ASEBA data, 3 endorsed clinically significant symptoms of depression, and 1 participant endorsed clinically significant symptoms of ADHD.

Individuals with autism and co-occurring ADHD, anxiety, or depression were included, while those with other psychiatric diagnoses within the past five years or co-occurring neurogenetic syndromes were excluded. Stimulant medication use was screened for before study participation, but there were no exclusionary criteria based on this. Of our 184 participants, 36 endorsed 'Yes' to taking medications and of these, 11 (all Autism) reported using stimulant medication. In our adult subgroup, ten autistic adults (26%) reported taking antidepressant medications, and in our children/adolescents subgroup, ten autistic participants' parents (22%) reported their child taking antidepressant medications.

2.3.1.1 Adults

Thirty-eight adult participants with autism (21 male; mean age = 27.65) and 58 neurotypical (NT) adults (36 male; mean age = 32.69) were included in the study. All adult participants were between the ages of 18 and 59 years and achieved full-scale IQ scores of ≥ 70 as measured by the Wechsler Abbreviated Scale of Intelligence-Second Edition (Wechsler, 2011) (WASI-II). Autism diagnoses were confirmed by the clinical judgment of a licensed psychologist on the research team specializing in the assessment of autism, supported by research-reliable administration of the Autism Diagnostic Observation Schedule-2 (ADOS-2; Lord et al. 2012).

Exclusion criteria for both groups included the presence of other neurological and genetic disorders, non-autism-related sensory impairments (e.g., uncorrected visual or hearing impairments), and substance/alcohol abuse or dependence during the past two years. Further, individuals in the NT group were excluded if they had reported a previous psychiatric history, cognitive or sensory impairment, use of psychotropic medications, or clinically elevated scores on the Social Communication Questionnaire (Rutter et al., 2003) (SCQ Total score > 15).

2.3.1.2 Children/Adolescents

Forty-five autistic children/adolescents (35 male; mean age = 11.53) and 43 neurotypical (NT) children/adolescents (34 male; mean age = 11.86) were included in the study. All child/adolescent participants were between the ages of 8 and 17 years and achieved full-scale IQ (FSIQ) scores of ≥ 70 as measured by the WASI-II. Autism diagnoses were confirmed by the clinical judgment of a licensed psychologist specializing in the assessment of autism, supported by research-reliable administration of the ADOS-2 and, when available, parent interviews ($n = 30$) that included algorithm items from the Autism Diagnostic Interview, Revised (ADI-R) (Lord et al., 1994).

Exclusion criteria for children/adolescents were similar to those for adults with some additional considerations. Mainly, for children and adolescents, behavior and co-occurring psychiatric conditions were screened for using parent and guardian reports.

2.3.2 Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki, and all participants were compensated $20 per hour of their time following each session. Written informed consent or assent forms were signed by all participants, while informed consent was obtained from parents or guardians of minors. All methods and procedures were approved by the Institutional Review Board for human subjects at Vanderbilt University Medical Center and carried out following relevant guidelines and regulations on ethical human research.

2.3.3 Measures

The Social Responsiveness Scale–Second Edition (SRS-2) was used to measure autistic traits dimensionally across the full sample. Adult participants in both diagnostic groups completed the SRS-2 adult self-report form, whereas parents or guardians of children/adolescents in both groups completed the analogous caregiver-report questionnaire, the SRS-2 School Age form. To facilitate comparison across the different groups, the SRS-2 total scores were converted to T- scores (M = 50, SD = 10).

2.3.3.1 Empathy

Empathy was assessed multi-dimensionally using an adapted version of the Multifaceted Empathy Test, the MET-J (Poustka et al., 2010), a validated performance-based test that separates cognitive and emotional empathy based on responses to emotional faces presented with- and without- a social context in the background. The original MET includes 50 still images depicting emotionally charged facial expressions of 25 positive (e.g., joy, happiness) and 25 negative (e.g., sadness, anger) emotions. The adapted MET-J version used in the present study included only 16 images each for positive and negative valence. The photographs are taken from the International Affective Picture System (IAPS), a well-validated database of photographs designed for standardized emotion and attention testing (Lang et al., 1997). In each trial, participants viewed an emotional image and were first asked to rate their level of arousal, followed by explicit emotional empathy ratings, and a cognitive empathy (i.e., emotion recognition) multiple choice question. Figure 2.1 depicts an example trial on the task, recreated using a free-use stock image from the Canva.com image database.

As described by Dziobek et al. (2008), to minimize demands of self-reflection and thereby also mitigate social desirability bias, we included an implicit assessment of emotional empathy by asking participants to rate how calm/aroused the emotional stimuli made them feel using the Self-Assessment Manikin (SAM). The SAM is a visual-analog scale providing scores ranging from 1 (very calm) to 9 (very aroused). Thus, for each picture, participants were asked (1) "How excited does this picture make you" (implicit emotional empathy; subsequently described as arousal empathy); (2) "While looking at the picture, how much do your feelings match the X's feelings" (emotional empathy; EE) measured on a visual Likert scale (1–9); and finally (3) "How does this X feel?" (cognitive empathy; CE). Here an "X" represents the noun used to describe the individuals (boy/girl/ man/woman) in the image, who varied across trials. Each trial ended with a final presentation of the emotional stimulus that provided feedback for the cognitive empathy question by displaying the correct emotion label from among the four choices. Note that this order and wording for EE surveys are slightly different from the original MET and MET-J, which provided feedback on CE surveys before presenting explicit emotional empathy surveys. We adapted this order to ensure that EE and arousal responses were made as reflexively as possible to the perceived emotion upon initial presentation, rather than being adjusted based on CE feedback. All stimuli were presented as slides of variable duration (ad libitum) in random order on a black screen.

2.3.4 Statistical Analyses

Differences in demographics (e.g., age, sex, verbal intelligence quotient, performance intelligence quotient) and SRS-2 scores were compared between the autism and NT groups within a Bayesian framework. When the outcome of interest was categorical (e.g., correct or incorrect emotion recognition), group differences were examined using a Bayesian analog of the Pearson chi-squared test (Gûnel and Dickey, 1974; Jamil et al., 2017). When the outcome of interest was a continuous variable (e.g., age), we examined mean differences using a Bayesian analog of the Welch (unequal-variances) t-test (Kruschke, 2013). Effect sizes from each of these tests (i.e., Cohen's d and the odds ratio [OR]) were summarized as the posterior median and 95% highest-density credible interval (CrI). Additionally, for all group comparisons, evidence for or against the point null hypothesis (H_0 ; i.e., no differences between groups) was quantified with a Bayes factor (Jamil et al., 2017; Wagenmakers et al., 2010), defined as the ratio of how likely the data are under the alternative hypothesis (H_1 ; i.e., the difference between the two groups is nonzero) divided by how likely the data are under H_0. In concordance with widely-used guidelines on Bayes factor interpretation (Harold, 1961; Wagenmakers et al., 2011), we considered BF10 values > 3 as indicating substantial evidence for H_1, BF_{10} values < 0.333 as indicating substantial evidence for H_0, and BF_{10} values between 0.333 and 3 as providing inconclusive and only "anecdotal" evidence for H_0 or H_1. All group comparisons were performed in the R statistical computing platform using open-source R code (Williams, 2020).

To determine the effects of various predictor variables on arousal, emotional, and cognitive empathy while controlling for possible covariates, we used R (Team, 2018) to analyze the data at the single-trial level using hierarchical Bayesian modeling. Trial-level MET data for arousal, emotional, and cognitive empathy were analyzed using (generalized) linear mixed effects models ([G]LMEMs), which allowed us to model the correlations between responses derived from the same participants as well as the same stimuli (Baayen et al., 2008). LMEMs were used to model arousal and emotional empathy, as the 9-item scale used to derive these outcomes had enough points to be approximated as a continuous variable (Rhemtulla et al., 2012). However, we used a logistic GLMEM to model cognitive empathy, as individual trial data from this part of the task consisted of binary "correct/incorrect" responses. The baseline [G]LMEM for each MET-derived outcome included fixed effects of age group (child vs. adult), sex, autism diagnosis, and emotional valence (positive vs. negative), as well as random intercepts for participant and stimulus (see example below for CE, Eq. 2.1).

Random slopes were also included in this baseline model for all subject-level predictors, allowing the effects of age group, sex, and autism status to vary by the stimulus. The decision to treat age as categorical in the BMA was driven by the finding that performance on the CE task increased with age throughout childhood, reaching an asymptote at approximately age 18–20, thereby indicating a difference between children and adults rather than a true linear age trend.

$$CE = Dx + AgeGroup + Sex + Valence + (1|Participant) + (1 + Stimulus|DxGroup + Sex + AgeGroup) \tag{2.1}$$

Where CE is cognitive empathy, and Dx is diagnostic group. For each of the three outcomes, we additionally determined if several other predictors beyond the baseline model contributed to task performance, including the two-way and three-way interactions between age, diagnosis, and valence; verbal IQ (VIQ); performance IQ (PIQ); and overall level of autistic traits (SRS-2 T-score). To determine whether any given predictor should be added to the baseline model, we fit candidate models that included all combinations of potential predictors (n = 40 potential models including the baseline). Then, using bridge sampling (Gronau et al., 2017), we calculated the marginal likelihood of each candidate model, deriving posterior model probabilities in a manner equivalent to the process of Bayesian model averaging (Hinne et al., 2020). The model with the highest posterior probability was considered the final model for each outcome. Using these model weights, we also computed inclusion Bayes factors (BF_{inc}; Hinne et al. 2020), allowing us to determine the degree of evidence for or against the inclusion of each predictor in the model. Inclusion Bayes factors are interpretable in the same manner as BF_{10}, with H_0 being the exclusion of the variable from the model and H_1 being the inclusion of the variable in the model.

Once the final model for each outcome was selected, we additionally tested all regression slopes in a Bayesian framework, using the 95% CrI to determine whether each slope was likely to be nonzero in magnitude. If the full 95% CrI excluded zero, we rejected the point null hypothesis that the effect was exactly zero. However, because this point null hypothesis is always false at the population level (Gronau et al., 2017), we also tested these effects for practical significance (Kirk, 1996). The Bayesian framework allows for a probabilistic view of the parameter estimates so that we can infer whether an effect is practically meaningful at the population level. This is done by defining a region of practical equivalence (ROPE) (Kruschke and Liddell, 2018), an interval of parameter values considered small enough to be equivalent to zero in practice (in this case β_{Std} = [-0.1, 0.1] for linear models and $e^{\beta Std} = [0.909, 1.10]$ for logistic models). Evidence both for and against the true parameter value falling within the ROPE can be quantified by calculating a ROPE Bayes factor (BF_{ROPE}), defined as the odds of the prior parameter distribution falling within the ROPE divided by the odds of the posterior effect size distribution falling within the ROPE (Makowski et al., 2019a,b). These Bayes factors can be interpreted on the same scale as previously discussed for BF_{10} and BF_{inc} (Harold, 1961; Wagenmakers et al., 2011). In the case that a parameter was nonzero or a given variable was included within the final model but the BF_{ROPE} value was smaller than 0.333, we considered this variable as not predicting the MET outcome of interest to a practically meaningful extent. Lastly, to assess the predictive power of the final model, we calculated the Bayesian R^2 coefficient proposed by Gelman et al. (2019).

All Bayesian [G]LMEMs were fit in Stan using the brms R package (Bürkner, 2017, 2018) with weakly informative priors, including Normal(0, 1) priors on all (standardized) regression slopes and intercept terms, as well as default half Student t_3(0, 2.5) priors on the standard deviation of each random slope or intercept term. Model parameters were estimated via Markov chain Monte Carlo (MCMC) using the No U-turn Sampler implemented in Stan (Hoffman and Gelman, 2014), with posterior distributions of each parameter estimated using 21,000 post-warmup MCMC draws from seven Markov chains (14,000 in cases where missing data were present). Parameter summaries from these posterior distributions were operationalized as the posterior median and the 95% CrI. Convergence for each model was confirmed by examination of Markov chain trace plots, as well as values of the Gelman–Rubin (Rubin & Gelman, 1992) convergence diagnostic $<$ 1.01. Missing data were handled using five-fold multiple imputations based on the random forest imputation algorithm implemented in the missForest R package (Stekhoven and Bühlmann, 2012; Stekhoven, 2013).

2.4 Results

2.4.1 Demographics

In total, 184 participants were included in the analysis sample: 45 children and adolescents (35 male; mean age = 11.53) with autism, and 43 neurotypical children and adolescents (34 male; mean = 11.86), 38 adults with autism (21 male; mean age = 27.65), and 58 neurotypical adults (36 male; mean age = 32.69). The two diagnostic groups were approximately equivalent in terms of sex ratio (OR = 1.091, 95% CrI [0.583, 2.003], BF_{10} = 0.177), although they significantly differed with respect to age (d = 0.457 [0.146, 0.773], BF_{10} = 22.2), full-scale IQ (d = 0.532 [0.224, 0.846], BF_{10} = 94.4), VIQ (d = 0.657 [0.326, 1.010]), and SRS-2 T-scores (d= -2.896[-3.478,-2.349]). Additionally, the NT group had numerically higher PIQ scores on average than the autistic group, although the Bayes factor indicated only "anecdotal" evidence in favor of a group difference (d = 0.284 [-0.021, 0.588], BF_{10} = 1.59).

2.4.2 Hierarchical Bayesian Models

Model selection procedures indicated that cognitive empathy scores were best predicted by a model including all baseline predictors and VIQ score ($P(M_{BL+VIQ}|Data) = 0.405$; $R^2_{Bayes} = 0.257[0.242, 0.272]$).The posterior inclusion probability of VIQ was relatively high (P_{VIQ} = 0.734), although the inclusion Bayes factor for VIQ did not meet the a priori threshold of 3 (BF_{inc} = 2.76). Inclusion Bayes factors also provided substantial evidence against the inclusion of all interaction terms, PIQ, and SRS-2 T-score as predictors of cognitive empathy (Table 2.1).

In the best-fitting model, autism diagnosis was associated with a practically significant reduction in performance on cognitive empathy (CE) trials (OR = 0.726, 95% CrI [0.587, 0.906], BF_{ROPE} = 3.70). This effect of group on CE is depicted in Fig. 2.1A. Moreover, age group was an even larger predictor of performance, with children across both diagnostic groups displaying significantly lower emotion recognition accuracy than adults (OR = 0.604 [0.462, 0.795], BF_{ROPE} = 37.80). Neither female sex (OR = 1.113 [0.917, 1.352], BF_{ROPE} = 0.110) nor negative valence (OR = 0.545 [0.267, 1.071], BF_{ROPE} = 1.609) significantly predicted performance on the cognitive empathy trials, although there was insufficient evidence to conclude that valence was unrelated to the chance of a correct response. Lastly, although higher VIQ significantly predicted higher performance on cognitive empathy trials (OR = 1.126 [1.037, 1.218] per standard deviation increase in VIQ), there was substantial evidence that this effect was too small to be practically significant (BF_{ROPE} = 0.213).

When predicting emotional empathy, model selection procedures indicated that the most likely model included all baseline predictors as well as the interaction between diagnosis and valence. Inclusion Bayes factors supported only the inclusion of diagnosis × valence interaction term in the final model (BF_{inc} = 5.59), along with the exclusion of most other predictors (Table 2.1).

The best-fitting model displayed a large effect of valence, with lower reports of shared feelings for negative emotions (β = -0.647 [-0.800,-0.489], $BF_{ROPE} = 4.89 \times 10^5$), as well as small and practically insignificant main effects of diagnostic group (β = -0.059 [-0.255, 0.142], BF_{ROPE} = 0.057), sex (β = -0.073 [-0.275,0.138], BF_{ROPE} = 0.072), and age group (β = 0.025 [-0.175,0.2124], BF_{ROPE} = 0.042). The interaction between diagnosis and valence was statistically significant, although the ROPE Bayes factor was equivocal concerning its practical significance (β = 0.188 [0.066, 0.307], BF_{ROPE} = 1.075). Although both diagnostic groups reported empathizing more with positive than negative emotions, this difference was larger in the NT group (d = 0.647 [0.489, 0.800]) than the autism group (d = 0.459 [0.315, 0.614]). This interaction is depicted in Fig. 2.2B.

When predicting ratings of arousal, the best-fitting model was found to include all baseline predictors as well as the interaction between age group and valence ($P(M_{BL+Age*Valence}|Data) = 0.677$; $R^2_{Bayes} = 0.466[0.451, 0.480]$). Inclusion Bayes factors demonstrated strong support for the inclusion of the age group × valence interaction (BF_{inc} = 147), as well as the exclusion of all other potential predictors (Table 2.1). Coefficients in the best-fitting model indicated practically insignificant effects of autism diagnosis (β =-0.045 [-0.232,0.145], BF_{ROPE} = 0.046), age (β = 0.084 [-0.118,0.289], BF_{ROPE} = 0.079), sex ($beta$ = -0.024 [-0.234,0.179], BF_{ROPE} = 0.048), and emotional valence (β = -0.137 [-0.342,0.071], BF_{ROPE} = 0.160). However, these effects were qualified by a statistically and practically significant interaction between age and valence (β = -0.269 [-0.390,-0.149], BF_{ROPE} = 16.3). Across both diagnostic groups, children reported significantly higher arousal ratings for positive stimuli compared to negative stimuli (d = 0.403 [0.195, 0.609]), whereas no significant effect of valence was seen in adult participants (d = 0.137 [-0.071, 0.342]). This interaction effect is illustrated in Fig. 2.3.

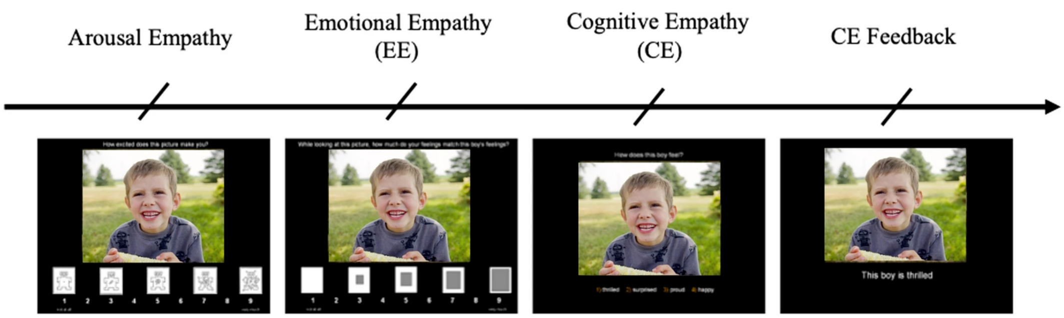

Figure 2.1: Example trial for ‘thrilled’ emotion depicted on MET-J task.
The surveys read 1) “How excited does this picture make you” (implicit emotional empathy/arousal empathy), 2) “While looking at the picture, how much do your feelings match the boy’s feelings (emotional empathy; EE, and 3) “How does this boy feel?” (cognitive empathy; CE). Cognitive empathy emotion label options are 1) thrilled, 2) surprised, 3) proud, 4) happy. The slides for this trial example were designed on PowerPoint using a free-use stock image from the Canva.com image database.

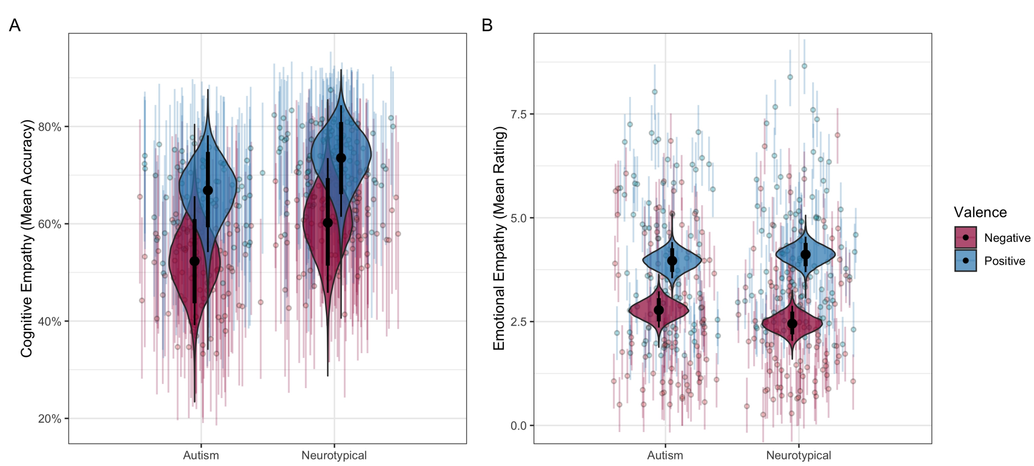

Figure 2.2: Group comparisons for (A) mean accuracy in emotion recognition for cognitive empathy surveys, and (B) mean resonance rating for emotional empathy surveys.

2.5 Discussion

Using a multidimensional approach, this study is consistent with previous findings of practically equivalent levels of emotional empathy between autistic and NT groups despite a significant effect of diagnosis on cognitive empathy. These findings also complement Dziobek et al. (2008), by extending the comparison

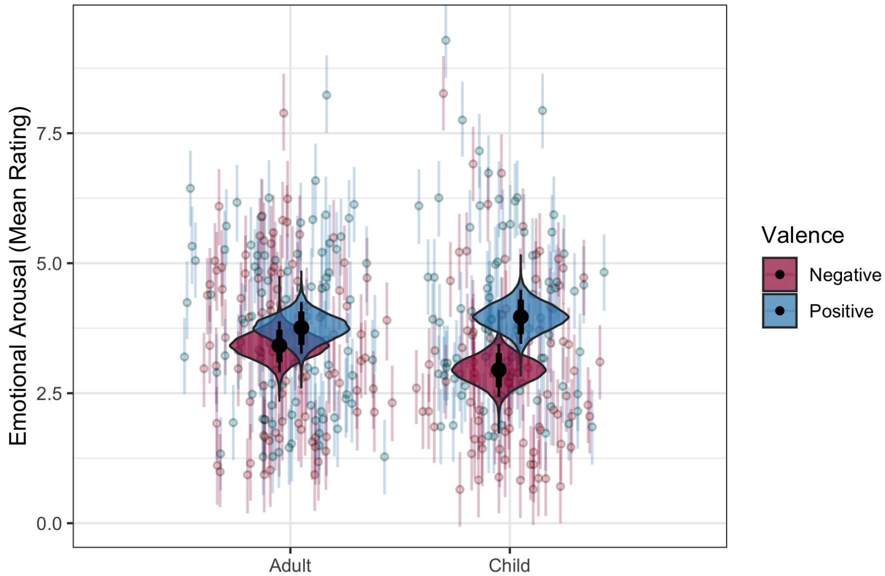

Figure 2.3: Age group comparisons for mean emotional arousal ratings to positive and negative emotionally charged facial expressions.

to test for valence effects. To our knowledge, only one other group has assessed emotional valence effects in autism using the MET (Mazza et al., 2014), which reported that autistic adolescents displayed reduced emotional empathy for facial expressions of negative emotions compared to controls, a difference that was not present for positive emotions. Notably, the findings of Mazza and colleagues differ from those of the current study, which found that ratings of emotional empathy were approximately equal between groups for negatively-valenced stimuli, although neurotypical individuals provided higher average ratings for positively-valenced stimuli. The present study further extends Mazza et al. (2014), results by assessing age group effects and utilizing a substantially larger child/adolescent autism sample. With regards to age, our Bayesian analysis indicates that children and adolescents across both diagnostic groups had greater difficulty with emotion recognition than adults, although the main effect of the age group on self-ratings of arousal and emotional empathy was small and practically insignificant.

Valence effects in our analyses were only significant in models predicting emotional empathy and arousal. For emotional empathy, the significant interaction between valence and diagnostic group indicated that positive facial expressions elicited greater emotional resonance than negative facial expressions across both groups, but that this difference was greater in neurotypicals compared to autistic individuals. In the arousal empathy Bayesian Model Averaging (BMA) analysis, the small and practically insignificant main effects for emotional valence and age group were qualified by a strong and practically significant interaction between these predictors. That is, the increase in arousal elicited by positive facial expressions relative to negative ones was more pronounced in our child and adolescent group compared to the adult group.

In the current study, we observed higher ratings for shared feelings to positive versus negative facial expressions that interacted with the diagnostic group but not with age. This may reflect a neurotypical advantage for better self-other distinction for negative valence compared to autistic individuals that persists across age. In other words, contrary to previous reports of unequivocally intact emotional empathy in autism (Dziobek et al., 2008; Baron-Cohen, 2011), emotional empathy may differ somewhat in autism when valence is considered. The contrast between greater resonance to positive emotions compared to negative emotions across neurotypical development may also be partially attributable to the effect of positivity biases for ambiguous emotions. In some neurotypical adults, ambiguous facial expressions like 'surprise' tend to get rated as positive, an effect that seems to be moderated by the regulatory influence of the prefrontal cortex (Tottenham et al., 2013). Thus, the lower degree of separation between emotional resonance ratings to positive and negative emotions in autism may also be reflecting neural differences in top-down emotion processing.

Supporting the cognitive vs. affective empathy dichotomy, Cox et al. (2012) reported distinct intrinsic functional connectivity (FC) dynamics in healthy adult brains for self-reported cognitive and emotional empathy. Using a difference score (cognitive–emotional), this group found emotional empathy dominance (negative scores) to be associated with stronger functional connectivity between social-emotional brain regions like the amygdala and ventral anterior insula (Cox et al., 2012). By contrast, cognitive empathy dominance (positive scores) correlated with greater FC in areas like the ventral anterior insula and superior temporal sulcus, both of which have been implicated in social-cognitive processes (Cox et al., 2012; Fan et al., 2013; Gu et al., 2015). This distinction also becomes relevant when considering the implications of valence-specific evidence for empathy differences in autism, like impairments in the ability to understand when social experiences warrant resonating with negative emotions, a feature that has been linked to aggressive behaviors (Eisenberg and Miller, 1987; Miller and Eisenberg, 1988; Pouw et al., 2013).

The present study had various strengths and limitations to consider. Amongst the strengths, our study included a wide age range in which we were able to replicate previous findings from research conducted primarily in adolescent and adult samples and extend findings to a larger group of younger individuals. Additionally, the use of robust statistical approaches allowed us to report on the practical significance of our findings as well as to test for equivalence between diagnostic groups on these empathy measures. Ours is among the first to combine several important approaches in a single study: examining empathy multidimensionally, testing both children and adults, and examining positive and negative emotional valence separately. These advances facilitate a significant step forward in our understanding of empathy in autism.

This study was limited by the exclusion of individuals with low IQ (FSIQ < 70) to ensure understanding of the task instructions. Future efforts to address this limitation should include objective psychophysiological empathy measures that do not require an explicit behavioral response or abstract thinking. An additional limitation is the fact that the current study did not include measurements of trait alexithymia (Bagby et al., 2020), which has been proposed to mediate the relationship between diagnoses of autism and performance on tasks tapping multiple facets of empathy (Fletcher-Watson and Bird, 2020; Bird and Cook, 2013; Bird and Viding, 2014). Another limitation is that we did not measure prosocial behavior propensity and interrogate how emotional resonance and emotional concern may contribute to prosocial tendencies. In retrospect, we would have also liked to complement our findings by including at least one additional validated empathy questionnaire to compare and enrich our understanding of multimodal empathy assessment.

It should also be noted that a growing literature further improving ecological validity by utilizing dyadic conversational interactions (typically involving richer but less emotionally charged stimulation than the static but highly emotional faces used in the MET) has described a "double empathy" problem with assumptions made from empirical research in empathy and autism (Milton, 2012; Edey et al., 2016; Morrison et al., 2020). These reports critique the use of neurotypical people as a reference point and conclude that differences are diminished when autistic individuals are partnered with one another, suggesting that an empathy deficit (at least in the relatively emotionally neutral context of an initial conversation with a new person) should be reframed as a feature of the interaction rather than the individual 55. Finally, The MET utilizes static emotional faces, which limits the ecological validity of the task. Following the example of recent studies that use dyadic interactions to characterize social differences in autism (Morrison et al., 2020; Qualls and Corbett, 2017; Rolison et al., 2015), future studies should continue to balance ecological validity with experimental control under a framework that does not assume a neurotypical reference point.

The self-report nature of the MET's design, albeit task-based, still confers some susceptibility to social desirability biases. This is one potential explanation for the increased emotional relatedness feelings reported by our neurotypical adult sample, who may be more impacted by social desirability bias (Kirchner et al., 2012). The specificity of this difference in facial expressions depicting positive emotions and not negative emotions, however, warrants further investigation. Future efforts should aim to collect more implicit measures of emotional empathy such as skin conductance, spontaneous facial expressions, and neural measures of empathic response. Within the context of conflated definitions and methodologies employed in previous research, the resulting confusion from conflicting academic reports on the autistic 'empathy deficit' has not been without effect on the autistic population. Over-generalizations on this matter have been described as 'unwarranted' and 'dehumanizing' by autistic self-advocates (Cohen-Rottenberg, 2013). Because of this negative impact potential, future work should also take great care to develop methodologies based on clearly defined empathy concepts as well as reporting and interpreting results using a more humane framework.

In conclusion, the current study finds autism differences in specific components of empathy. We report impaired cognitive empathy in autism, a valence by diagnostic group effect in emotional empathy, and a valence by age group effect for arousal empathy. In both diagnostic groups, emotion recognition as measured by our cognitive empathy survey was significantly greater in adults than in children and adolescents. Improved emotion recognition by adulthood across groups may reflect lifelong practice effects from both typical social settings and training effects of social interventions. Further investigations would benefit from an analysis that accounts for potential confounds like co-occurring mental health symptoms or training effects on the ability of individuals with autism to recognize emotions. Our empathy findings suggest that emotionally charged stimuli, specifically hedonically negative stimuli, may be actively recruiting separate perceptual pathways that are distinctly altered in autism. Thus, better elucidating how specific components of empathy are affected in autism is crucial for informing target-specific social interventions seeking to improve empathic capacities and social outcomes.

Table 2.1: Bayesian Modeling Results

Cognitive Empathy					
Best Fit Predictor	OR [95% CrI]	BF_{10}	BF_{inc}	BF_{ROPE}	P_{ROPE}
Diagnosis (Autism)	**0.726 [0.587,0.906]**	**6.854**		**3.677**	**0.00**
Sex (F)	1.113 [0.917,1.352]	0.179		0.110	0.00
Age group (Child/Adolescent)	**0.604 [0.462,0.795]**	**58.271**		**37.80**	**0.00**
Valence (Negative)	0.545 [0.267,1.071]	1.633		1.609	0.00
Verbal IQ Z-score	1.126 [1.037,1.218]	2.949	2.760	0.213	0.00
Emotional Empathy					
Best Fit Predictor	β [95% CrI]	BF_{10}	BF_{inc}	BF_{ROPE}	P_{ROPE}
Diagnosis (Autism)	-0.059 [-0.255,0.142]	0.121		0.057	0.594
Sex (F)	-0.073 [-0.275,0.138]	0.135		0.072	0.544
Age group (Child/Adolescent)	0.025 [-0.175,0.214]	0.103		0.042	0.671
Valence (Negative)	**-0.647 [-0.80,-0.49]**	**1.61×10^{-6}**		**4.89×10^{5}**	**0.000**
Diagnosis x Valence	0.188 [0.066,0.307]	3.521	5.59	1.075	0.076
Arousal Empathy					
Best Fit Predictor	β [95% CrI]	BF_{10}	BF_{inc}	BF_{ROPE}	P_{ROPE}
Diagnosis (Autism)	-0.045 [-0.232,0.145]	0.104		0.046	0.653
Sex (F)	-0.024 [-0.234,0.179]	0.110		0.048	0.640
Age group (Child/Adolescent)	0.084 [-0.118,0.289]	0.143		0.079	0.517
Valence (Negative)	-0.137 [-0.342,0.071]	0.253		0.160	0.345
Age group x Valence	**-0.206 [-0.390,-0.149]**	**89.300**	**147**	**16.3**	**0.005**

Practically significant predictors for each empathy component are shown in ***bold****.*

CHAPTER 3

Identifying and Describing Subtypes of Spontaneous Empathic Facial Expression Production in Autistic Adults[1]

3.1 Introduction

Within the socio-emotional domain of autism symptoms, the capacity to understand and use nonverbal communication is central to developing and maintaining healthy social relationships throughout the lifespan (Decety and Jackson, 2006) and facilitates learning and workforce outcomes (Johnson and Johnson, 1997). Persistent social difficulties translate to difficulties developing and maintaining social relationships throughout adulthood and are associated with depression, anxiety, loneliness, and isolation (Volkmar et al., 2014). Given the pervasiveness and impact of socio-emotional difficulties in autism, many social skills intervention programs are designed to facilitate training in socially relevant nonverbal cue usage, production, and understanding through in-person and technology-based paradigms (Soares et al., 2021). Beyond providing structured opportunities to learn and practice social skills, these programs have been shown to improve social metrics like friendship quality, and social functioning, and to reduce feelings of loneliness in youth and adult autistic groups (Gates et al., 2017; Spain and Blainey, 2015).

Though they are not yet considered standard-of-care, emerging automated technology systems supported by machine learning have facilitated the administration and improved the accessibility of autism services like social skills interventions (DiPietro et al., 2019). Supervised and unsupervised machine learning approaches hold promise for predicting outcomes and facilitating the identification of clinical subgroups based on symptom profiles (Jacob et al., 2019). Current applications for computational methods in autism research include diagnostic methods (Song et al., 2019a), the analysis of facial expression production (Gordon et al., 2014; Leo et al., 2018), and behavioral and physiological signals (Sharma et al., 2017). Facial expression production and reciprocity are key components of socio-emotional constructs like emotional regulation (Gross and John, 2003) and the success of social interactions (Halberstadt et al., 2001). Within the autistic population, facial expressions are found to be different in appearance metrics like social congruence, frequency, or duration (Trevisan et al., 2018). In practice, these differences may lead to negative evaluations from peers and reduce the overall quality of social interactions (Stichter et al., 2010). Interestingly, previous reports do not suggest that facial expression intensity is affected in autism (Keating and Cook, 2021), despite prevalent clinical descriptions of both "flat affect" (Capps et al., 1993; Stagg et al., 2014) and "exaggerated" expres-

[1]Parts of this chapter have been adapted from "Identifying and Describing Subtypes of Spontaneous Empathic Facial Expression Production in Autistic Adults", published in *Journal of Neurodevelopmental Disorders* and has been reproduced with the permission of the publisher

sions (Faso et al., 2015; Wozniak et al., 2017). One possible explanation is that within autistic populations, distinct subgroups of extreme high and low levels of expressivity average one another out and mask group differences that are not uniform in direction. Computational approaches such as k-means clustering can help to differentiate this scenario from a true lack of group difference in facial expression intensity.

3.1.1 The Present Study

The symptomatic heterogeneity in autism suggests a need for more adaptive and personalized social skill intervention programs. Empathy has long been considered a sub-domain of the social communication difficulties present in autism (Harmsen, 2019), but more current evidence suggests a much more nuanced picture (Quinde-Zlibut et al., 2021) given the multi-faceted nature of empathy measurement. Advanced social skill interventions programs would benefit from a more concrete and empirical understanding of the different expressiveness profiles within the autistic population (e.g., "flat affect" vs. "exaggerated" or "inappropriate" facial expressions as measured by gold standard diagnostic instruments) and how they differ from neurotypicals (NT) before deploying facial expression production and reception training. To this end, we cluster autistic and neurotypical adults separately based on their facial expressions within the socially relevant context of empathy.

3.2 Methods

Our primary objective for this paper was to explore whether the altered patterns of facial expression production metrics in autism reflect the dynamic and nuanced nature of facial expressions or a true diagnostic difference. To this end, we collected facial videos during an experimental study, derived a set of automated facial expression features from the videos using the iMotions affect recognition toolkit (iMotions, 2021), and applied an exploratory unsupervised learning approach on the feature sets for our autistic and NT participants separately to derive interpretable clusters.

3.2.1 Participants

A total of 84 participants, originally part of a larger study, were included in this analysis. The current sample ($n = 84$) consisted of 27 autistic participants (12 female, 14 male, 1 other) and 57 neurotypical (NT) participants (21 female, 36 male). All participants in this sample were adults between the ages of 18 & 59 years. Participants were pre-screened using the Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-II) Wechsler (2011), with Full Scale IQ (FSIQ) scores ≥ 70. Participants also completed the Social Responsiveness Scale-2 (SRS-2), a self-report questionnaire that measures autistic traits Constantino and Gruber (2012).

Autism diagnoses for participants were confirmed by the clinical judgment of a licensed psychologist specializing in the assessment of autism, supported by research-reliable administration of the Autism Diagnostic Observation Schedule-2 (ADOS-2) Lord et al. (2012). Exclusion criteria for both our autistic and NT groups included the presence of other neurological and genetic disorders, non-autism related sensory impairments (e.g., uncorrected visual or hearing impairments), and substance/alcohol abuse or dependence during the past two years. Further, individuals in the NT group were excluded if they had reported a previous psychiatric history, cognitive or sensory impairment, use of psychotropic medications, or clinically elevated scores on the Social Communication Questionnaire (Rutter et al., 2003). Individuals with autism and co-occurring ADHD, anxiety, or depression were included, while those with other recent psychiatric diagnoses within the past 5 years or co-occurring neurogenetic syndromes were excluded. All participants provided informed consent and were compensated $20 per hour of their time following each session. All procedures were approved by the Institutional Review Board for human subjects at Vanderbilt University Medical Center.

3.2.2 Study Procedure

We captured participants' facial expressions while they completed an adapted version of the Multifaceted Empathy Test (MET) (Dziobek et al., 2008), a validated multidimensional computer-based task that separates arousal, emotional, and cognitive components of empathy. A full description of the MET can be found in Quinde-Zlibut et al. (2021); briefly, the adapted version presently used includes 32 emotionally charged photographs depicting positive and negative scenarios and is known as the MET-J (Poustka et al., 2010). When presented with each image, participants were asked to rate their level of arousal, emotional relatedness (emotional empathy), and finally to label the emotion (i.e., emotion recognition) via a multiple choice question (cognitive empathy).

In the present study, the task was designed to be compatible with the iMotions v.6 computer software platform for biosensor integration (iMotions, 2021). The facial expressions of interest for the cluster analysis were recordings from emotional empathy trials where participants viewed an emotional image (of either positive or negative valence) and were asked to answer: *"While looking at the picture, how much do your feelings match the boy's feelings?"*. Note that while the previous example is for a photograph of a boy, the task included standardized and validated images of males and females of all ages from the International Affective Picture System (Lang et al., 1997).

3.2.3 Data Collection

All participants in the MET study worked individually in the same well-illuminated testing room using a webcam-enabled laptop, which facilitated the collection of facial videos. The videos were processed *post hoc* using the iMotions AffDex SDK. The AffDex engine works by detecting 33 points around major facial landmarks (e.g., eyes, nose, mouth, etc.; Figure 3.1), tracking and analyzing them throughout stimuli presentation to identify and classify 20 'facial action units' (AUs; e.g., upper lip raise, outer brow raise) (McDuff et al., 2016). Likelihood scores are computed based on the probability that detected AUs are equal to evaluations made by a human rater. Facial expressions or AUs with probabilities below 10% are considered to be of high uncertainty and are thus given likelihood scores of 0. The algorithm, based on Ekman & Friesen's Emotional Facial Action Coding System (EMFACS) (Ekman and Friesen, 1978b), then uses combinations of these facial AUs to compute likelihood scores for the presence of 7 core emotions (joy, anger, fear, disgust, contempt, sadness, and surprise), and summary metrics like, *facial engagement/expressiveness* and *emotional valence*. The AffDex channels of interest, derived from the video frames at a frequency of 30Hz, are further defined below:

1. *Engagement/Expressiveness:* A general measure of overall facial expressiveness, computed as the average of the highest evidence scores from upper *(Brow raise, Brow furrow, Nose wrinkle)* and lower face region *(Lip corner depressor, Chin raise, Lip pucker, Lip press, Mouth open, Lip suck, Smile)*, respectively.

2. *Valence:* A measure of the affective quality of the facial expression, i.e., how positive or negative the associated emotion is. Increased positive valence was determined in AffDex by high likelihood of AUs like *Smile and Cheek Raise*, while increased negative valence was determined by high likelihood of AUs like *Inner Brow Raise, Brow Furrow, Nose Wrinkle, Upper Lip Raise, Lip Corner Depressor, Chin Raise, Lip Press and Lip Suck*.

The decision to focus on these summary metrics was made *a priori* to maximize objectivity and avoid confounds related to assumptions about emotion. Likelihood scores for AUs offer a more concrete and interpretable metric across clinical groups than emotion scores. AffDex scores for AUs typically recruited for expressions of joy (smile) and anger (brow furrow) were found to be significantly correlated to the corresponding EMG metrics (zygomaticus mayor/corrugator supercilii) (Kulke et al., 2020). We decided against comparing groups based on emotions (e.g., joy, sadness) because AffDex validation studies suggest that the algorithm's classification of emotion channels is still too premature for comparative use (Stöckli et al., 2018; Magdin et al., 2019). Further, the autism-specific FACS and electromyography (EMG) literature is still scant and inconclusive (Weiss et al., 2019; Mathersul et al., 2013b)- making it difficult to develop hypotheses regarding how specific AUs are recruited in this population. Derived from individual AUs, summary metrics allow for group comparisons without making assumptions about emotional states underlying specific facial expressions, which may vary by group. Thus, we decided to assess facial expression in terms of overall

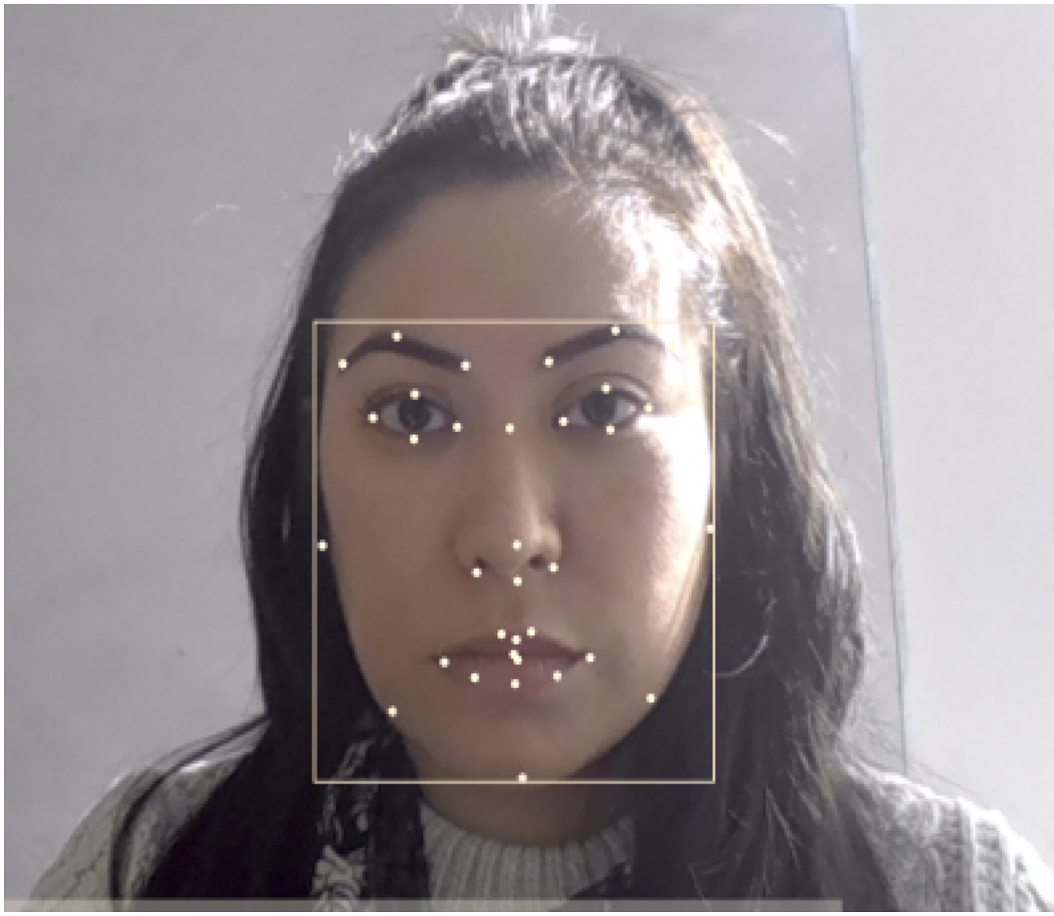

Figure 3.1: Example of the 33 AffDex detected points around the major landmark facial features. Note that the two points between the lips is one point that was captured during slight movement.

production (i.e., overall AUs activated in response to stimuli) and appropriateness (i.e., overall congruence of AUs activated in response to stimuli).

3.2.4 Approach for Clustering the Autism & NT groups

3.2.4.1 Feature Selection

For each group (NT & autism), we constructed a set of four features from the data processed through iMotions. The features, listed below, reflect overall levels of facial expressiveness and emotional valence of participants under two different experimental conditions: *(a) When they responded to images evoking positive emotion valence*, and *(b) When they responded to images evoking negative emotion valence*. For each participant, we computed the average peak expressiveness and valence scores across trials depicting images of positive and negative emotional valence.

1. Expressiveness ($-$): Average peak expressiveness score for images with negative valence.

2. Expressiveness (+): Average peak expressiveness score for images with positive valence.

3. Valence (−): Average peak emotion valence score for images with negative valence.

4. Valence (+): Average peak emotion valence score for images with positive valence.

The *coefficient of variation* ($\frac{SD}{Mean}$) was computed for each constructed feature, as a variance-based feature selection criterion. All four features had coefficients of variation $> 20\%$, and were included for clustering. Contrary to values from the engagement channel (which range from 0-100), values from the valence channel range from -100-100 with negative values indicating negative affect, 0 indicating neutral affect, and positive scores indicating positive affect. Thus, to avoid any potential order-of-magnitude-related feature biases within groups, each feature was Z-score standardized across participants. This was done to account for range differences in participants' responses between the engagement and valence variables and prevent higher values from unduly influencing clusters.

3.2.4.2 K-Means Clustering

A K-means algorithm was applied on the processed feature set of each group (autism & NT) using the k-means implementation available in the *cluster* package (Maechler et al., 2021) in the R environment for statistical computing Team (2018). K-means is a distance-based algorithm that clusters data points based on how similar they are to one another. Similarity is defined as the Euclidean distance between points such that the lower the distance between the points, the more similar they are. Likewise, the greater the distance, the more dissimilar they are (Leonard and Rousseeuw, 1990). In practice, the K-means algorithm clusters data points using the following steps:

1. *Choice of an optimal value for k clusters:* For the present analysis we used the total within sum of squares (WSS) method. This involves comparing how the WSS changes with increasing number of clusters and identifying the number of clusters associated with the biggest drop in WSS. In our case, the optimal number of clusters determined by this method was $k = 2$ for both the autism and NT cluster analyses.

2. *Random assignment of each data point to an initial cluster from 1 to K:* This step involves matching each participant with the closest centroid in an n-dimensional space where n corresponds to the number of features (in this case $n = 4$).

3. *Centroid Recalculation:* After participants are assigned to k clusters, the centroids are recalculated as the mean point of all other points in the group.

4. *Cluster Stabilization:* Steps 2 and 3 are repeated until participants are no longer reallocated to another centroid.

In order to validate assumptions made about the variance of the distribution of each attribute, the resulting clusters were visually assessed for linear boundaries, and based on their *average silhouette widths*, a measure of how similar each data point is to its own cluster compared to other clusters. Positive silhouette (Si) values indicate appropriately clustered data (the closer to 1, the better the data was assigned). Negative Si values indicates inappropriately clustered data while Si values of 0 indicate that the data point falls between two clusters.

The stability of the resulting clusters was assessed by bootstrap resampling of the data without replacement and computing the Jaccard similarities of the original clusters to the most similar clusters in the resampled data. Jaccard similarity values measure the ratio of points shared between two clusters and the total number of points across both clusters. The mean over the bootstrap distribution of similarity values serves as an index of the stability of the cluster and is henceforth referred to as the Jaccard Index (JI) (Hennig, 2007). Clusters yielding Jaccard Index values < 0.6 are considered to be highly unstable, between 0.6 and 0.75 to be indicative of patterns within the data, ≥ 0.75 to be valid and stable, and ≥ 0.85 to be highly stable (Hennig, 2008). One hundred bootstrap resampling runs were carried out in R using the **clusterboot** function in the *fpc* package (Hennig, 2020) and the **kmeansCBI** interface function corresponding to our clustering method.

3.2.5 Within Group Comparisons

Within groups, clusters were compared using a robust, non-parametric effect-size statistic, Cliff's delta (Cliff, 1993; Feng and Cliff, 2004) using the *orddom* package (Rogmann, 2013) in R. Delta does not require any assumptions regarding the shape or spread of two distributions and estimates the probability that a randomly selected observation from one distribution is larger than a randomly selected observation from another distribution, minus the reverse probability. Possible delta (δ) values range from -1 to 1, where values of 0 indicate a complete overlap of groups and values of -1 or 1 indicate that all the values in one group are larger than all the values in the other.

Our variables of interest for this analysis included age, average peak engagement/expressiveness, average emotion congruence, and all the SRS-2 subscales. Average peak engagement/expressiveness was calculated as an average of the expressiveness scores to both negative and positive images. Average congruence was calculated as the average number of instances when a participant's valence scores matched the emotional valence of the MET images (i.e., when the valence score was greater than 0 and the image was positive, the facial expression was marked as congruent). This metric was calculated across trials as a more intuitive measure of how appropriate participants' facial expressions were in relation to the valence of the stimuli.

3.2.6 Between Group Comparisons of Stable Clusters

For the purpose of determining whether there is a true difference in facial expressiveness, we conducted autism-NT group comparisons on the stable sub-types identified through the separate autism and NT cluster analyses. Separate robust ANOVAs were computed for average peak engagement and average valence. This analysis was implemented in R using the **bwtrim** function in the *WRS2* package (Mair and Wilcox, 2020). Briefly, the function adopts a between-within subjects design (i.e., one between-subjects variable and one within-subjects variable) to identify effects based on trimmed means. The trimmed mean discards a specified percentage of values at both ends of a distribution, providing an alternative to the arithmetic mean that is less sensitive to outliers. For both dependent variables, the between-within subjects ANOVA was calculated on the 10% trimmed mean.

3.2.7 Exploratory Analyses

Finally, we ran exploratory correlation tests between average engagement and the emotion recognition scores from the MET-J study (Quinde-Zlibut et al., 2021), overall ADOS-calibrated severity scores, and SRS subscales (social cognition and social awareness) to better understand the relationship between these variables.

3.3 Results

3.3.1 K-means Clustering

3.3.1.1 Autism Cluster Analysis

The k-means model identified two clusters (further characterized in Fig 3.2a) within our autism sample (N = 27). The autism clusters were assessed visually (Fig 3.3a), by silhouette (Si) analysis, and the Jaccard Index (JI):

1. Cluster 1 (n = 19) with an average Si of 0.56 and JI = 0.886

2. Cluster 2 (n = 8) with an average Si of 0.14 and JI = 0.759

Subgroup comparisons revealed that Cluster 1 differed from Cluster 2 in average engagement/expressiveness ($\delta = 0.934, p < .001$), and average congruence ($\delta = -0.434, p = 0.035$). Cluster 2 was therefore characterized as a less stable (Si=0.14), more exaggerated group whose facial expressions were less congruent with the stimulus' emotional valence (Fig 3.4a). The clusters did not differ in age or any SRS-2 subscale (Table 3.1).

3.3.1.2 NT Cluster Analysis

The k-means model identified two clusters (further characterized in Fig 3.2b), within our NT sample (N=57). The NT clusters were assessed visually (Fig 3.3b), by silhouette (Si) analysis, and the Jaccard Index (JI) :

1. Cluster 1 (n=39) with an average Si of 0.55 and JI = 0.858

2. Cluster 2 (n=18) with an average Si of 0.20 and JI = 0.762

Subgroup comparisons revealed that Cluster 1 differed from Cluster 2 in average engagement/expressiveness ($\delta = 0.940, p < .001$), and average congruence ($\delta = -0.625, p < .001$). Cluster 2 was therefore also characterized as a less stable (Si=0.20), more exaggerated group whose facial expressions were less congruent with the stimulus' emotional valence (Fig 3.4b). The clusters did not differ in age or any SRS-2 subscale (Table 3.2).

The group of NTs that appear on the edge of the convex hull in Cluster 1 reflect participants who on average displayed minimal expressivity/engagement in response to emotionally charged stimuli. We refrained from excluding these participants in subsequent analyses because we felt that minimal engagement scores in this NT cluster would be informative compared against the more stable autism cluster.

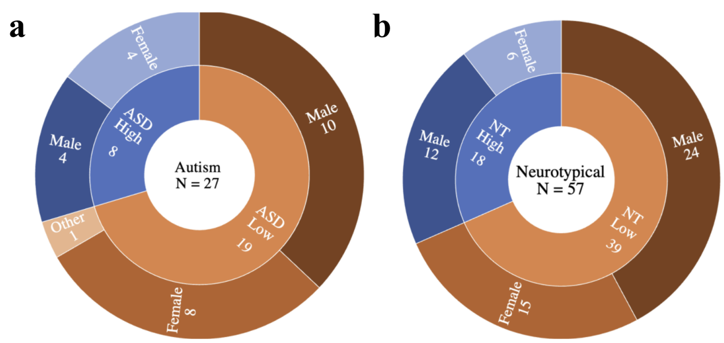

Figure 3.2: K-means Clusters by Group

Number of (a) autistics (ASD; n = 27) and (b) neurotypical (NT; n = 57) adults in each cluster grouped by engagement (High, Low) and gender (Male, Female) Brown/tan: Cluster 1, Blue: Cluster 2

3.3.2 Comparison of the Stable Autism and NT Clusters

We selected and compared the two more stable subgroups within our autism and NT samples to identify whether these differed in average congruence, facial expressiveness, and valence in response to emotional images. We found no group difference in average congruence across images ($\delta = 0.09, p > .05$). For expressiveness/engagement, the between-within trimmed-means ANOVA revealed a significant difference between groups ($F(1, 38.58) = 5.02, p = .03$; Fig 3.5a), no within group effect of image valence ($F(1, 47.59) = 0.54, p > .05$; Fig 3.5b), and a non-significant group by image valence interaction ($F(1, 47.59) = 0.27, p > .05$). The between-within trimmed-means ANOVA fit for the valence of facial expressions in response to

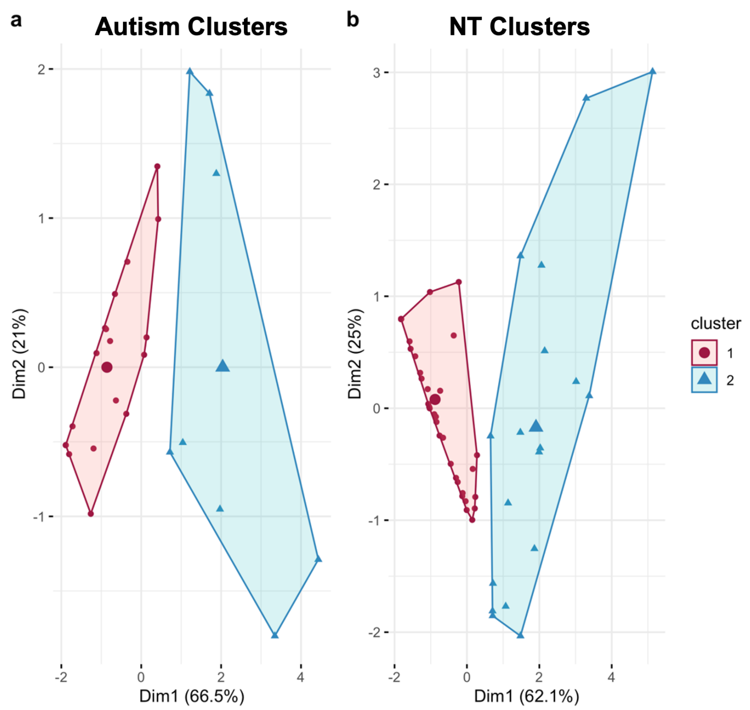

Figure 3.3: Clusters found in (a) autistic (n=27) and (b) NT adults (n=57)

The autism cluster analysis revealed a larger more stable cluster (Cluster 1, n = 19) and a smaller, less stable cluster (Cluster 2, n=8). The NT cluster analysis revealed a larger more stable cluster (Cluster 1, n=39) and a smaller, less stable cluster (Cluster 2, n=18).

emotional images did not reveal significant between group differences $F(1,33.44) = 3.78, p > .05$), within group differences in response to positive versus negative images $F(1,33.14) = 1.98, p > .05$), or a group by image valence interaction $F(1,33.14) = 1.39, p > .05$).

3.3.3 Exploratory Analyses

Within group correlations between average engagement and emotion recognition suggests that in autism, higher expressivity/engagement is associated with poorer performance in the emotion recognition component of the MET-J study ($\rho = -0.45, p = 0.05$). We observed a weaker and opposite trend in the NT group of increased emotion recognition performance with more expressivity/engagement ($\rho = 0.20, p > 0.05$; Fig 3.6). Average expressivity/engagement was not correlated to ADOS-calibrated severity scores ($\rho = -0.13, p > 0.05$), the social cognition ($\rho = 0.11, p > 0.05$), or social awareness ($\rho = 0.06, p > 0.05$) subscales of the SRS-2 in our stable autism sample.

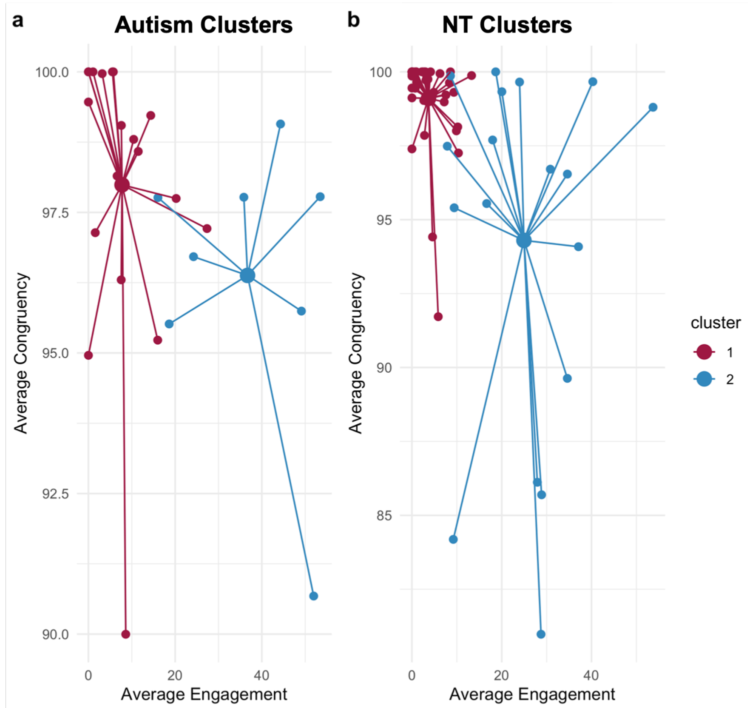

Figure 3.4: Average congruence and expressiveness/engagement scores found in (a) autistic and (b) neurotypical adult clusters.

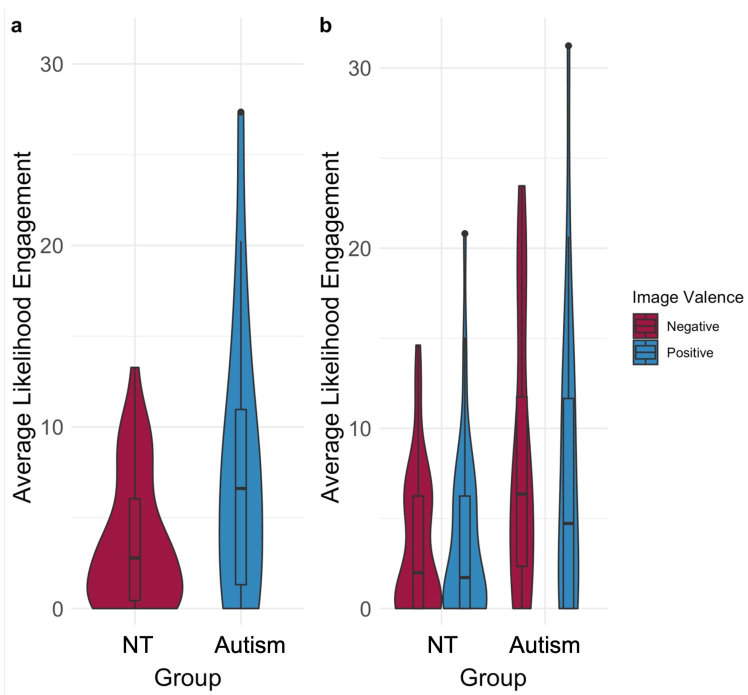

Figure 3.5: Average expressiveness/engagement scores found (a) between stable groups across images and (b) within stable groups in response to negative and positive images.

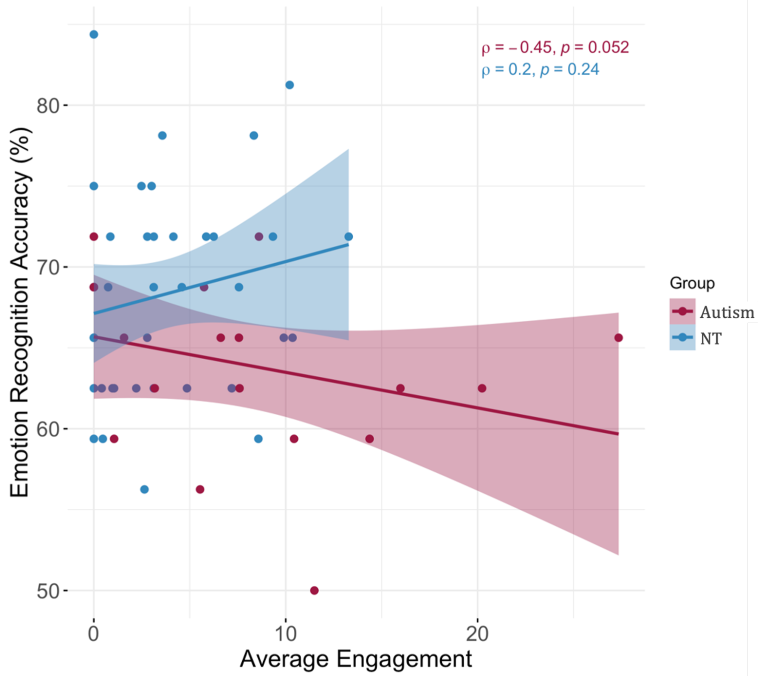

Figure 3.6: Correlations between emotion recognition accuracy (%) and average engagement across all emotional images for autistic and NT participants in the more stable clusters.

3.4 Discussion

Our main finding was that a subset of autistic adults in our sample show heightened spontaneous facial expressions regardless of image valence. We used automated facial coding and a clustering approach to limit inter-individual variability that may have otherwise obscured group differences in previous studies, allowing an "apples-to-apples" comparison between autistic and neurotypical adults. We did not find evidence for greater incongruous (i.e., inappropriate) facial expressions in autism. Taken together, our self-report and expressivity findings point to a higher degree of facial expressions recruited for emotional resonance in autism that may not always be adaptive (e.g., experiencing similar emotional resonance regardless of valence). These findings build on previous reports indicating that facial expression intensity is not diminished in autism, and suggest the need for intervention programs to focus on emotion recognition and social skills in the context of both negative and positive emotions. These findings are further discussed in relation to current literature in the sections to follow.

In this study, a primary goal was to use computational approaches to address discrepancies in the literature on spontaneous empathic facial expressions in autistic adults. Facial expression as a means of registration and communication of emotion is a highly nuanced behavioral phenomenon characterized by high inter-individual variability (Holberg et al., 2006) and strong developmental effects (Profyt and Whissell, 1991). The literature is further complicated by the use of a variety of research methods, with drastic differences in the method of eliciting facial expressions (ranging from explicitly asking participants to produce a facial expression to eliciting spontaneous expressions with a nonsocial (e.g., a foul odor) or a social (e.g., another face making an expression) stimulus). Studies also differ in the method of measuring facial expressions (ranging from coding by observers who may or may not have formal training in facial coding (Ekman and Friesen, 1978b), to electromyography of facial muscles, or automated algorithms for coding facial action). Thus, methodological and individual variability has presented a challenge to a clear understanding of how facial expression production differs in autism. A recent meta-analysis (Trevisan et al., 2018) found that, across various approaches, autistic people on average appear to differ on the quality and frequency of facial expressions, but are largely similar to neurotypicals in the intensity and timing of facial expressions. However, given that the studies in those analyses included a range of the aforementioned variations and noted moderating effects of individual factors, there is still a considerable lack of clarity on the effect of autism on spontaneous empathic facial expressions specifically, which are more likely to relate to empathy than elicited/requested expressions or spontaneous expressions to non-social stimuli.

For this reason, we focused on spontaneous facial expressions to images depicting an emotional face–a variant of facial mimicry. We restricted our sample to adults and used automated facial coding to capture participants' spontaneous facial expressions when viewing images of other people in emotionally charged situations. These data were then subjected to clustering analyses to isolate reliable subgroups based on overall levels of facial expressiveness or engagement. We found that both autistic and non-autistic adults could be separated into two clusters: a larger cluster with relatively lower overall expressivity and more within-cluster homogeneity in the recruitment of spontaneous facial expressions, and a smaller cluster that exhibited higher expressivity overall but with significant variability between individuals in the cluster.

To limit the potential for inter-individual variability in this nuanced behavior to obscure meaningful differences, we used only the larger and more stable cluster in each group for subsequent group analyses. Our three primary findings in this subset were surprising. First, the autistic group showed *higher* overall facial engagement or expressivity in response to the emotional images, without significant effects of image valence or an interaction between image valence and group. Second, counter to predictions based on the appropriateness of facial expressions to the social situation, the two groups did not differ on congruency (the extent to which the participant's facial expression matched that in the image) or in their valence experience in response to either positive or negative images. Finally, in the autistic adults, higher levels of facial expressivity were *negatively* related to accuracy in the emotion recognition task, while a weaker trend was opposite in direction for the neurotypical group. We will explore each of these findings below.

Our primary finding that a sample of autistic adults, from which a small cluster of variable but highly expressive individuals was already removed, still showed higher levels of facial expressivity in response to emotional images. This finding is consistent with reports of intact facial mimicry in autism (Schulte-Rüther et al., 2017), more intense spontaneous facial expressions in adolescents with autism during non-social contexts **?**, as well as with the findings of a large meta-analysis (Trevisan et al., 2018) demonstrating that autistic individuals do not show diminished intensity of facial expressions across contexts. Indeed, we find that in the context of spontaneous response to emotionally charged images, autistic adults on average respond with more facial expressivity. In our previous work using the same stimuli (Quinde-Zlibut et al., 2021), both groups experienced greater self-reported emotional resonance (i.e., emotional empathy) to positive versus negative images. There was also significantly less differentiation between self-reported emotional resonance to positive versus negative emotional images in our autistic group. For this reason, we expected interactions between group and valence in spontaneous facial expressions, which are thought to reflect emotional resonance/empathy. However, we did not detect any interactions, suggesting that these spontaneous facial expressions may represent more than simply a reflection of emotional resonance.

The presence of subgroups and group differences based on intensity and congruence of facial expressions in both the neurotypical and autistic samples without the accompanying differences in the congruence or appropriateness of facial expressions between the two more stable clusters suggest a possible role for individual differences in the affective and sensorimotor aspects of facial expression production. Motor programs to produce a spontaneous facial expression in response to an emotional image may be initiated as expected, suggesting intact feedforward input from amygdala to facial motor circuitry (Gothard, 2014). However, in autistic adults, the end result of executing this program is an amplified facial expression, which could reflect altered use of sensory feedback from facial skin and muscle to both facial motor and affective brain regions.

While we did not find significant relations between clinical variables such as ADOS calibrated severity scores or SRS subscale score and our main outcome measure of facial engagement, we noted an interesting dichotomy in the way that facial engagement associates with accuracy of emotion recognition on the MET-J. For the autistic group, higher facial engagement/expressivity was related to *lower* emotion recognition (i.e., cognitive empathy). One interpretation of this unexpected finding is that increased facial expressivity is an effect, rather than a cause, of social difficulty. As adults engage in a task that is challenging to them—identifying the emotions of another person—increased facial engagement could arise from increased concentration or worry (Rozin and Cohen, 2003). An alternative interpretation is that amplified facial expressions may contribute to social difficulty. Previous studies suggest that these two interpretations may be mutually related; adults with autism are more tolerant of exaggerated emotional facial expressions than neurotypical adults, and this is thought to reflect a rule-based strategy employed by autistic adults when learning to interpret emotional facial expressions (Walsh et al., 2014), a process that may involve amplified facial mirroring in an attempt to learn the associations.

Limitations and Future Directions

Our finding of equivalent valence in the more stable clusters does not preclude a subset of individuals characterized by inappropriate or incongruous facial expressions, as is commonly described clinically in a minority of people on the spectrum. Indeed, the smaller and less stable cluster in our autism sample may represent this subset of the autistic population. A limitation of this study is the small sample size that prevented us from further defining this subgroup. Our small sample size also warrants well-powered follow-up studies to confirm the present results.

Other limitations of the study include the use of static stimuli rather than dynamic or interactive social stimuli, thus future work should consider alternative paradigms that more closely align with real-world social situations that elicit spontaneous facial expressions. We based our decision to derive within-group clusters on preliminary analyses demonstrating poor cluster assignment when the autism-NT data were pooled. While this lack of specificity for autism precludes classification, it points to the highly variable nature of facial expression use across our sample regardless of diagnostic status.

Algorithm-based metrics of emotion, trained on people without autism, are likely to lead to results that are not applicable to autism. We address this concern by limiting our choice of metrics to overall engagement and valence (distinct from AffDex-classified emotions like 'joy' or 'surprise') which are solely based on facial actions and compared against the probability that they are equal to scores from human coders. Future complementary studies should include complete FACS coding assessments of separate clusters to identify AU-specific differences. In this scenario, the combination of AFC, clustering, and FACS could reduce the amount of FACS coding hours considerably.

Currently, socio-emotional autism literature is dominated by top-down paradigms that do not address the inherent reciprocity in dyadic interactions (Milton, 2012; Edey et al., 2016; Morrison et al., 2020)- thereby limiting our understanding of social phenomena to a stereotypical "norm". Indeed, the presence of a smaller, more expressively variable cluster in our NT sample suggests that the expressivity patterns observed in the smaller autism cluster may not be so "atypical". Both the autism, and social skill intervention fields will benefit from future work that explores socio-affective phenomena from this less biased framework. Future studies should also examine this phenomenon in child and/or adolescent samples and individuals with co-occurring intellectual disability to better understand the influence of development and cognitive ability.

Table 3.1: Aggregated statistics on age, facial expressiveness, emotion congruency and social responsiveness survey (SRS-2) scores for the two autism clusters.

Variable	Autism: Cluster 1 (n=19)		Autism: Cluster 2 (n=8)		δ (95% CI)	p.value
	Median	SD	Median	SD		
Age (years)	25.97	9.75	22.50	4.36	-0.289 (-0.651, 0.18)	0.203
Expressiveness/Engagement	6.61	7.56	40.08	15.29	0.93 (0.731, 0.985)	**0**
Average Congruence	98.80	2.53	97.24	2.59	-0.434 (-0.736, 0.012)	**0.035**
SRS-2 (T-scores)a						
Social Awareness	61.00	10.42	57.50	13.73	-0.158 (-0.593, 0.349)	0.548
Social Cognition	63.00	10.51	68.00	10.51	0.388 (-0.121, 0.736)	0.103
Social Communication	69.00	11.34	64.00	13.99	-0.039 (-0.536, 0.477)	0.891
Social Motivation	71.00	11.4	64.00	15.15	-0.132 (-0.611, 0.419)	0.656
Restricted Interests & Repetitive Behaviour	73.00	12.36	67.50	16.45	-0.184 (-0.63, 0.353)	0.508

*p.values in **bold** indicate statistically significant differences between the clusters.*

Table 3.2: Aggregated statistics on age, facial expressiveness, emotion congruency and social responsiveness survey (SRS-2) scores for the two neurotypical (NT) clusters.

Variable	NT: Cluster 1 (n=39)		NT: Cluster 2 (n=18)		δ (95% CI)	p.value
	Median	SD	Median	SD		
Age (years)	29.63	7.68	32.42	13.12	0.099 (-0.281, 0.453)	0.615
Expressiveness/Engagement	2.79	3.69	25.95	12.61	0.94 (0.826, 0.98)	**0**
Average Congruence	99.72	1.64	96.62	6.16	-0.625 (-0.817, -0.308)	**0**
SRS-2 (T-scores)a						
Social Awareness	44.00	7.86	44.00	7.59	-0.038 (-0.349, 0.281)	0.822
Social Cognition	44.00	7.76	44.00	6.26	0.066 (-0.245, 0.364)	0.68
Social Communication	45.00	8.01	44.00	7.00	-0.096 (-0.402, 0.229)	0.565
Social Motivation	51.00	9.13	52.00	8.64	0.093 (-0.221, 0.39)	0.563
Restricted Interests & Repetitive Behaviour	45.00	6.04	47.00	9.93	0.189 (-0.152, 0.49)	0.268

*p.values in **bold** indicate statistically significant differences between the clusters.*

CHAPTER 4

The Neural Basis Of Cognitive Empathy in Autism

4.1 Introduction

There is now substantial empirical evidence for impaired cognitive empathy in autism. In our own study, discussed in Chapter II, we have used the Multifaceted Empathy Test-Juvenile (MET-J; Dziobek et al. 2008) to show lower accuracy of emotion recognition or emotion labeling of positive and negative human expressions in a large sample of broad age range (Quinde-Zlibut et al., 2021). Indeed, autism differences in behavioral indices of cognitive empathy like emotion recognition accuracy and theory of mind have been consistently reproduced across samples, contexts, and age groups (Dziobek et al., 2008; Mazza et al., 2014; Quinde-Zlibut et al., 2021; Kleinman et al., 2001). Efforts to elucidate neural correlates for these outcomes suggest that atypical cognitive empathy in autism is related to connectivity among brain regions implicated in subserving interoception, social-cognitive processes, and autonomic monitoring in neurotypical development (Frith and Frith, 2001; Decety and Jackson, 2004; Amodio and Frith, 2006; Schulte-Rüther et al., 2007; Fan et al., 2011; Cox et al., 2012; Shi et al., 2020).

Statistical and technological advancements in social neuroscience have made it possible to learn much about the neural correlates of empathy through structural MRI (Banissy et al., 2012), and functional connectivity MRI (Fan et al., 2011). Task-based functional connectivity studies in autism suggest that regions showing different connectivity patterns during cognitive empathy tasks are functionally important for cognitive and emotional processes like assessing external inputs for affective importance and value (anterior insula & anterior cingulate cortex; Fan et al. 2013; Lockwood 2016), emotion recognition, mimicry, and understanding (inferior frontal gyrus; Iacoboni 2005; Shamay-Tsoory 2011), self-other social referencing (temporoparietal junction; Frith et al. 2003; Saxe and Kanwisher 2004; Quesque and Brass 2019), and making socially and emotionally informed decisions (amygdala & ventromedial prefrontal cortex; Amodio and Frith 2006; Adolphs 2010).

Much of what we know about a possible core empathy network comes from functional MRI studies that interrogate empathy using performance-based MRI tasks that capture state rather than trait capacities (Uribe et al., 2019). The distinction between state and trait is much like that of climate and weather, one describing long-term patterns in weather conditions and the other describing short term atmospheric changes, respectively. While both capture important personality concepts, traits make up characteristic patterns of people's thoughts, feelings, and behaviors that generalize across similar situations and experiences. On the other hand, states are patterns of thought, feelings, and behavior in response to very specific and particular situations (Schmitt and Blum, 2020). Thus, as the literature supporting a core empathy network that differs in autism grows, it is difficult to ascertain what findings are generalizable to concepts and situations more common to people's everyday life and what is confined to the controlled nature of the lab setting.

Resting state functional connectivity (rs-FC) measures the temporal correlation of spontaneous blood oxygenation level dependent (BOLD) activity in brain regions that are spatially separated (Woodward and Cascio, 2015). The BOLD neuroimaging technique measures the relative change in oxygenated and deoxygenated blood in the presence (task-based fMRI) or absence (rs-fMRI) of a task by detecting its magnetic susceptibility. In the absence of a task, rs-FC captures low frequency oscillations across brain regions that, if correlated, are assumed to be part of intrinsic networks of functional brain organization (Fox and Raichle, 2007; Woodward and Cascio, 2015). These intrinsic functional networks are thought to be established, at least in part, through experience over time and across contexts (Fair et al., 2009; Lewis et al., 2009; Zhu et al., 2011). The task-independent nature of this method also offers advantages for use in clinical populations like autism that may not be able to meet the cognitive demands of task-based fMRI (Fornito and Bullmore, 2010). Beyond capturing intrinsic properties that are more stable, allowing for a more generalized characterization of brain function, rs-FC also mitigates concerns about task-based confounds like motivation and performance influencing case- control group differences.

The aforementioned benefits and scarce extant rs-FC literature on cognitive empathy differences in autism motivated the present study. Thus, the first objective was to replicate previous task-based findings of group differences across the network of regions involved in cognitive empathy using resting state data. The second objective was much more exploratory- to gauge the behavioral relevance of distinct rs-FC patterns, we investigated how diagnostic group interacts with connectivity between specific region pairs to predict emotion recognition accuracy, our measure of cognitive empathy. In line with a small but growing body of literature reporting that differences in task-based network configurations are reflected at the intrinsic level (Smith et al., 2009; Tavor et al., 2016), we hypothesized that the FC patterns among empathy relevant regions would be more similar among individuals within but not across diagnostic group. Based on previous findings on impaired self-other distinction and mentalizing in autism (Bernhardt et al., 2014; Lombardo et al., 2010), we hypothesized that interactions between diagnostic group and the connectivity between cognitive regions like the TPJ and vmPFC would be most predictive of percent mean emotion recognition accuracy.

4.2 Methods

4.2.1 Participants

Participants in this study were from a pool of participants in a larger and longitudinal lab study who agreed to be recontacted and who were recruited from the community through social media and flyers. The present sample (*n* = 76) consisted of 37 Autism (27 males, ages 8-35) and 39 participants with neurotypical development (26 males, ages 8-34) who completed the MET as previously reported in Quinde-Zlibut et al. (2021). All participants were pre-screened using the Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-II) (Wechsler, 2011), for full-scale IQ scores greater than or equal to 70. Autism diagnoses were confirmed by the clinical judgment of a licensed psychologist specializing in the assessment of autism, supported by research-reliable administration of the ADOS-2 and, when available, parent interviews that included algorithm items from the Autism Diagnostic Interview, Revised (Lord et al., 1994).

Exclusion criteria for both groups included the presence of other neurological and genetic disorders, non-autism related sensory impairments (e.g., uncorrected visual or hearing impairments), and substance/alcohol abuse or dependence during the past two years. Further, individuals in the NT group were excluded if they had reported a previous psychiatric history, cognitive or sensory impairment, use of psychotropic medications, or clinically elevated scores on the Social Communication Questionnaire (SCQ Total score 15) (Rutter et al., 2003).

4.2.2 Cognitive Empathy

Participants completed an adapted version of the well-validated computer-based Multifaceted Empathy Test, the MET-J as described in Quinde-Zlibut et al. (2021). Briefly, the test involves presenting participants 32 images of male- and female- human expression from the International Affective Picture System (IAPS) (Lang et al., 1997). The set of images included both positive and negative emotionally charged expressions across a broad age range. After viewing each image, participants were asked a set of three questions designed to parse out emotional (EE) and cognitive empathy (CE). Emotional empathy was assessed by asking participants to rate their level of arousal and rate their level of emotional resonance (i.e., “how much do your feelings match the boy’s feelings”). Cognitive empathy was assessed by asking participants to label the emotion of the human expression via multiple choice. As this is the one aspect of empathy that has been consistently reported to be a challenge in autism, CE measured as percent mean emotion recognition accuracy, was the behavioral outcome of interest in the present study.

4.2.3 Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and all participants were compensated $20 per hour of their time following each session. Written informed consent or assent forms were signed by all participants, while informed consent was obtained from parents or guardians of minors. All methods and procedures were approved by the Institutional Review Board for human subjects at Vanderbilt University Medical Center and carried out in accordance with relevant guidelines and regulations on ethical human research.

4.2.4 Neuroimaging Data Acquisition and Processing

Neuroimage data acquisition and processing took place in the Vanderbilt University Institute of Imaging Science Center for Computational Imaging XNAT (Har, 2016; Huo et al., 2018). Image processing followed closely after methods used in Huang et al. (2021).

4.2.4.1 Acquisition of Structural and Resting State Scans

High-resolution T1-weighted anatomical images were acquired via sagittal slices with 1mm3 voxel resolution, TR=8.0 msec, TE= 3.7 msec, flip angle = 70, and acquisition matrix = 256 x 256 x 170 on a Siemens Tim Trio 3T scanner with a 32-channel head coil.

Resting state images were acquired using an echo planar imaging (EPI) sequence (3x3x4 mm voxels, TR=2s, flip angle 79, and acquisition matrix 80 x 80 x 28) for approximately 6min 46s duration (203 volumes).

4.2.4.2 Neuroimage Pre-Processing

The Computational Anatomy Toolbox 12 (CAT12, version 12.5; http://www.neuro.uni-jena.de/cat/) was used to segment anatomical images into gray matter, white matter, and cerebrospinal fluid (CSF). Resting state scans were preprocessed in SPM12 and were (1) realigned to a mean scan, (2) co-registered with the native space structural scan, then (3) underwent resting-state denoising procedures: bandpass filter (0.01– 0.1 Hz), regression of CSF and white matter signal, regression of 12 motion parameters (6 translation and rotation parameters and their first derivative). All resting state scans went through a quality assurance procedure that included calculating framewise displacement (FD) and temporal signal to noise ratio (tSNR). Scans with a median FD > 0.5 were excluded from further analysis.

4.2.4.3 Region of Interest Masks

Given that cognitive empathy related processes are thought to occur through interactions and connectivity between limbic (emotional) and cognitive structures (Decety et al., 2012), our final mask included regions important for both cognitive and emotional processes. Left and right insular regions (posterior, mid, anterior) were generated using cytoarchitecturally-defined regions of interest (ROIs) defined by Farb et al. (2013). Left and right amygdala regions (centromedial, basolateral nuclei) were generated using the Juelich atlas (Amunts et al., 2005) in the FMRIB Software Library (FSL) by thresholding the corresponding maps at 50%. FSL offers a comprehensive tool library for analyzing MRI, fMRI, and diffusor tensor imaging (DTI) data. The left and right temporoparietal junction (TPJ) ROIs were generated using the anterior and posterior TPJ maps from the Mars et al. (2012) temporoparietal junction parcellation in FSL, thresholding at 50%. A small percentage of overlapping voxels were assigned to the anterior TPJ. Left and right inferior frontal gyrus maps (pars triangularis and pars opercularis) were generated using the Harvard-Oxford cortical atlas (Desikan et al., 2006) in FSL, thresholding the corresponding maps at 50%.

A single mask was generated for the left ventromedial prefrontal cortex (vmPFC), the dorsal anterior cingulate cortex (dACC) and right supplemental motor area (SMA) due to their proximity to midline. The left vmPFC map was generated from connectivity-based parcellations in Jackson et al. (2020), selecting for the ventral connectivity cluster (threshold at 80% intensity) and using available maps from NeuroVault, an open data repository for brain maps (https://neurovault.org/collections/4798/). The dACC and rSMA masks were generated as 8mm spheres from the peak activation coordinates for cognitive-evaluation > affective-experiential empathy and affective-perceptual empathy contrasts, respectively, in Fan et al. (2011).

4.2.4.4 Functional Connectivity

Functional connectivity was computed by Pearson correlating time series data between every pair of ROIs, resulting in 21 X 21 symmetric FC matrices.

4.2.5 Statistical Analyses

Differences in continuous (age, FSIQ), and count (sex) demographic variables were compared between the autism and control group using Welch's unequal variances t-test and chisq.test functions in the stats R package, respectively. The diagnostic group difference in emotion recognition accuracy (i.e., cognitive empathy) found in the larger study (Quinde-Zlibut et al., 2021) and reported in Chapter 2 was confirmed using Welch's unequal variances t-test.

4.2.5.1 Multivariate Distance Matrix Regression

Towards our first objective of confirming that the rs-FC network for cognitive empathy is different in Autism, we used the multivariate distance matrix regression (MDMR) approach (Anderson, 2001) to test the association between diagnostic group and the similarity in rs-FC patterns across our sample arranged and computed as a distance matrix (**D**). A motion parameter, median frame-wise displacement (FD), was also simultaneously tested and included in this analysis as a predictor of no interest. Association tests are achieved by decomposing the sums of squares of the distance matrix into a portion attributable to regression onto predictor variables (in our case diagnostic group and motion), and a portion due to residual. This analysis was carried out using the *MDMR* package in the R statistical software by passing the diagnostic group predictor and distance matrix outcome to the **mdmr** function.

In the context of this study, the MDMR method allowed us to study the association between diagnostic group and rs-FC measurement profiles while avoiding common challenges in traditional univariate general linear model methods like correcting for multiple comparisons by reducing the total number assessments required (Bennett and Miller, 2010; Shehzad et al., 2014). The procedure, as outlined by Anderson (2001), is a three-step process that includes:

1. Computing the distance between all pairs of individuals (N) with respect to a given set of dependent variables (e.g., patterns of brain connectivity) for obtaining a $N \times N$ distance matrix (D)
2. Calculating a PseudoF (Fp) statistic to test the hypothesis that one or more regressor variables (such as diagnostic group) have no relationship to variations in the distance or dissimilarity among individuals
3. Testing the significance of the Fp statistic using permutation tests.

The output of this analysis provides information on the pseudo proportion of explained variance (${R^2}_p$) and significance of each predictor. Because the F_p is analogous to an F-statistic from the standard ANOVA model, significant predictors with ${R^2}_p = k$ can therefore be interpreted as explaining k x 100% of the variation in the similarity of the individual connectivity patterns. The statistical significance of each predictor was calculated using a null distribution generated from 5,000 permutations.

4.2.5.1.1 Geodesic Distance- A Measure of (Dis)Similarity

We computed the distance matrix for MDMR using the geodesic distance metric of similarity. In geometry, a geodesic describes a curve that represents the shortest path between two points on a curved surface. There is extensive evidence that functional connectivity correlation matrices are objects that lie on non-linear, curved surfaces known as positive semidefinite cones (Boyd et al., 2004; Venkatesh et al., 2020; Abbas et al., 2021). Thus, Venkatesh et al. (2020) proposed the geodesic distance as a more geometry-aware approach to similarity indices of functional connectivity matrices (which are a specific example of a correlation matrix) that considers their non-linear properties.

A single geometry-aware distance matrix was generated for the connectivity matrices of all participants ($N = 76$) by adapting the **`distance_FC`** function found in https://github.com/makto-toruk/FC_geodesic.

Briefly, this involved wrapping the function within a nested loop that would compute and store the geodesic distance of any given matrix against itself and all other matrices. Pair-wise distances were arranged into a symmetric 76 x 76 distance matrix (D) for use in multivariate distance matrix (MDMR) regression.

4.2.5.2 Exploratory Regressions

Our second objective was to identify what region-to-region pairwise correlations explain more inter individual variance in percent mean emotion recognition accuracy, our measure of cognitive empathy with observed group differences. To do this we ran several linear regression models to test the interaction between diagnostic group and each pairwise correlation of interest using the **lm** function in the stats package. To minimize the total number of models to run, we selected pairwise correlations of regions that are consistently involved in cognitive empathy according to the literature (Schulte-Rüther et al., 2007, 2010). Except for the IFG regions (pars triangularis and pars opercularis), we averaged connectivity across hemispheres where possible. Since activity in the left IFG is consistently related to language and verbal capacities (Dapretto and Bookheimer, 1999; Haller et al., 2005; Hagoort, 2005), we included the average of right pars triangularis and right pars opercularis as right IFG only. Thus, the final list of regions included in this analysis are as follows: basolateral amygdala, anterior TPJ, posterior TPJ, left ventromedial prefrontal cortex, right inferior frontal gyrus, and anterior insula (see Table 4.1).

4.3 Results

There were no significant group differences in age (t = -1.81, p = 0.07), FSIQ (t = -1.42, p = 0.16), or sex ($X^2 = 0.12$, p = 0.73) in our autism-control comparisons. In this smaller subset of participants previously reported on in Quinde-Zlibut et al. (2021) and Chapter 2, we also found a significant group difference in emotion recognition accuracy (t = -3.29, p = 0).

4.3.1 Multivariate Distance Matrix Regression

Using the multivariate distance matrix regression (MDMR) approach we found that the rs-FC patterns among empathy-relevant regions are more similar for individuals within group (Autism-Autism, NT-NT) than individuals across groups (Autism-NT) (F_p = 0.017, p = 0.024, Figure 4.1). Motion was also significantly more similar within groups than across groups (F_p = 0.019, p = 0). The percentages of variance explained for each significant predictor, and for the total model were modest at best (1.6% for group, 1.8% for motion, and 3.5% for the total).

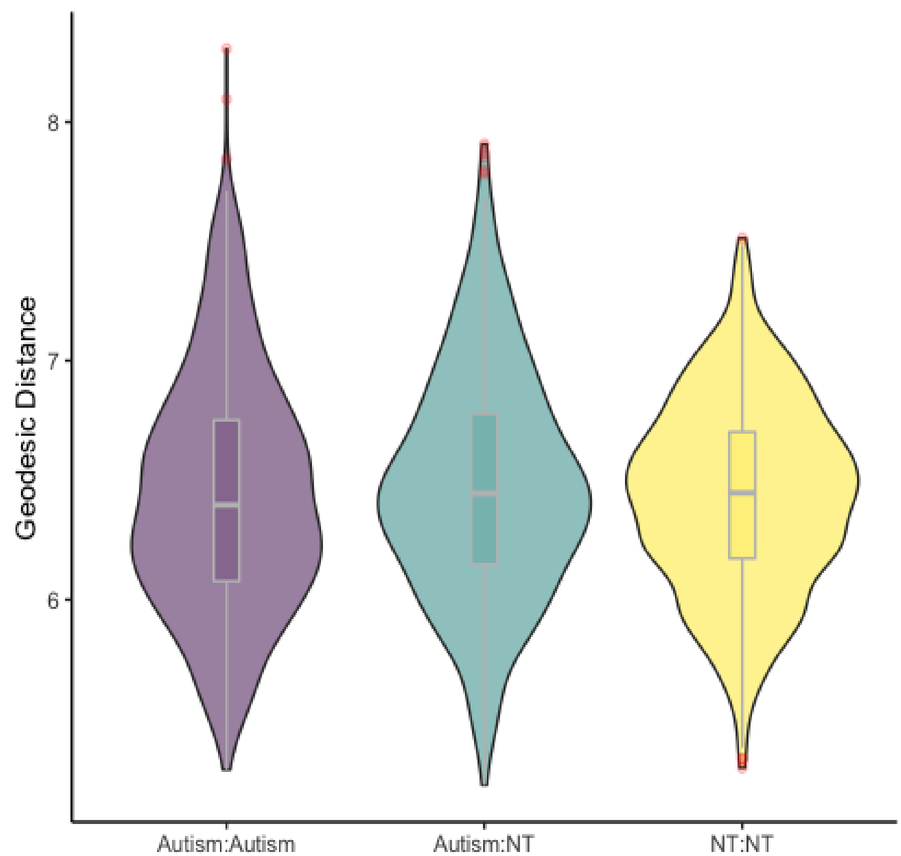

Figure 4.1: Geodesic distances by comparison group

4.3.2 Exploratory Analysis

To explore the behavioral relevance of a cognitive empathy network that is more similar among autistics compared to controls, we regressed emotion recognition accuracy, our measure of cognitive empathy, onto diagnostic group, 15 separate pairwise correlations (Table 4.1), and the interaction between group and each pairwise correlation. Of all the tested models, two had interaction terms that were significant predictors of emotion recognition accuracy:

$$EmotionRecognitionAccuracy = Dx + BLA : pTPJ + Dx * BLA : pTPJ \tag{4.1}$$

$$EmotionRecognitionAccuracy = Dx + BLA : rIFG + Dx * BLA : rIFG \tag{4.2}$$

Where Dx stands for diagnostic group, connectivity between two regions is represented with ‘:’, BLA stands for basolateral amygdala, pTPJ in (Eq. 4.1) is posterior TPJ, and rIFG in (Eq. 4.2) is right inferior frontal gyrus. In (Eq. 4.1) there was a significant diagnostic group by BLA:pTPJ interaction (t = -2.34,

p = 0.022), while the main effect for diagnostic group (t = 2.53 , p = 0.015) but not BLA:rIFG pairwise correlation (t = 1.51 , p = 0.135) was significant. In (Eq 4.2) there was a weak diagnostic group by BLA:rIFG interaction (t = -2.01, p = 0.048), while the main effect for diagnostic group (t = 3.24, p = 0.001) but not BLA:rIFG pairwise correlation (t = 1.43 , p = 0.157) was significant. Results for the remaining models in this exploratory analysis can be found in Table 4.1. Visual inspection of the geodesic distances by comparison indicates greater variability within the autism group (Autism-Autism) compared to between groups (Autism-NT) and within control group (NT-NT) distances. On average, the three comparison groups had similar distances yet the median distance score for Autism-Autism comparisons was slightly smaller (Figure 4.1).

4.4 Discussion

Using a combination of resting state functional connectivity and a geometry-aware metric of similarity, the geodesic distance, we found that the connectivity among regions important for cognitive empathy are more similar for individuals within the same diagnostic group than between diagnostic groups. Separately, our exploratory analysis for identifying neural correlates of emotion recognition in autism point to two potentially important pairwise relationships: connectivity between 1) the basolateral amygdala with the posterior temporoparietal junction and 2) the basolateral amygdala with the right inferior frontal gyrus. The role of these regions should be interpreted with caution, however, as we did not correct for the multiple tests performed in this exploratory step.

Our MDMR finding is consistent with previous neuroimaging studies that report autism specific connectivity patterns among empathy relevant brain regions (Shi et al., 2020). Visual inspection of the geodesic distances by comparison group provided additional insights to our MDMR results. Figure 4.1 suggests that the diagnostic group-specific similarity in connectivity is related to degree of variability such that Autism-Autism distances are more variable and still slightly more similar to each other than Autism-NT and NT-NT distances. We did find it surprising that the geodesic distances between the connectivity patterns of our autism and neurotypical participants were not much different than the differences observed within group for neurotypicals or autistics. Nevertheless, the presence of a task-independent connectivity profile in empathy relevant regions that is more similar among autistics points to a promising avenue for further elucidating autism specific connectivity using resting state methods of neuroimaging with low cognitive demands.

The multivariate MDMR method offers several advantages over traditional univariate strategies that test the association between phenotypic measures and only one functional connection at a time (Cole et al., 2010). Primarily, it avoids the need for conducting many statistical tests that increase the potential for false positive decisions by testing the simultaneous contributions of entire functional connectivity sets to phenotypic variables of interest. Thus, given that empathy is thought to be driven by patterns of synchronous activity across distributed brain regions, this multivariate approach likely offers a more accurate representation of the relationship between empathy-relevant connectivity and diagnostic phenotype (Varoquaux and Craddock, 2013; Shehzad et al., 2014). This advantage also circumvents the need to meet any a priori assumptions or limit the number of regions to assess making it possible to test various networks and thus serve as a guide for follow-up correlation studies with better regional specificity (Shehzad et al., 2014).

To this end, we conducted an exploratory analysis to identify potential candidates driving a rs-FC pattern among regions relevant for cognitive empathy that is more similar within than between groups. However, the present study does not have enough power to avoid the very same pitfalls that the MDMR approach overcomes, thus we cannot be sure that our findings from this secondary analysis would replicate. At best, we can speculate in our interpretation of these results that our autistic participants likely engaged a different neural strategy for emotion recognition that relies more on emotional-cognitive coupling than our neurotypical controls. A positive relationship between emotion recognition accuracy and the BLA connectivity with self-referential social cognitive regions like the pTPJ and rIFG in autism would suggest that autistic individuals access their own emotional states to better understand emotions in others.

Such a relationship would align with previous work reporting preferential recruitment of regions important for gaining access to information of the self during cognitive empathy tasks in autism Schulte-Rüther et al. (2010); Lombardo et al. (2010); Bernhardt et al. (2014). Thus, if autistic individuals tap into their own emotions during emotion recognition tasks, it follows that accuracy would decrease when there is a mismatch between felt and observed emotions. It also follows that the social consequences of such a mismatch would scale with increasingly complex emotions and warrants further investigation to better understand the developmental effects of emotion recognition using more dynamic and socially relevant stimuli.

4.4.1 Limitations and Future Directions

There are several limitations to the present study, some of which have been already acknowledged. Primarily, the MDMR multivariate approach for neuroimaging studies is an improvement over univariate tests but lacks regional specificity. While helpful for identifying potential network differences related to phenotypes, it is difficult to fine tune hypotheses to specific neural connections of interest. To do so would require well powered, region of interest-specific, follow-up studies. Our exploratory findings should be interpreted with caution and warrant further investigations on larger samples of a broad age range to replicate and extend the present study by addressing the effects of age, IQ, and sex on neural correlates of cognitive empathy abilities in autism. Future directions also include further elucidating the role of brain regions important for self-other distinction and testing for effects of laterality on emotion recognition strategies.

Table 4.1: Exploratory Regression Models

Independent Variables	**Coefficients B (SE)**	***t***	***p***	R^2adj	***F*(df)**	***p***
Intercept	55.22 (1.93)	28.616	0	0.126	4.61(3,72)	0.005
Dx	9.43 (2.60)	3.62	0.001			
BLA : AI	-22.32 (13.34)	-1.67	0.099			
Dx * BLA : AI	21.95 (17.66)	1.24	0.218			
Intercept	56.07(1.81)	30.92	0	0.1135	4.2 (3,72)	0.009
Dx	8.09(2.60)	3.11	0.003			
BLA : aTPJ	14.14(12.51)	1.51	0.252			
Dx * BLA : aTPJ	-6.07 (16.95)	-0.395	0.694			
Intercept	56.74(1.69)	33.49	0	0.157	5.66 (3,72)	0.002
Dx	6.29(2.53)	2.486	0.015			
BLA : pTPJ	20.97(13.86)	1.51	0.135			
Dx * BLA : pTPJ	-44.95 (19.182)	-2.34	0.022			
Intercept	56.91(1.79)	31.73	0	0.100	3.79 (3,72)	0.014
Dx	7.96(2.51)	3.18	0.002			
BLA : vmPFC	4.11(6.75)	0.61	0.544			
Dx * BLA : vmPFC	0.69 (11.17)	0.06	0.951			
Intercept	56.87(1.72)	33.15	0	0.140	5.09 (3,72)	0.003
Dx	7.74(2.39)	3.24	0.002			
BLA : rIFG	22.82(15.95)	1.43	0.157			
Dx * BLA : rIFG	-43.18 (21.47)	-2.01	0.048			
Intercept	57.51(2.82)	20.38	0	0.094	3.59 (3,72)	0.0176
Dx	6.84(4.34)	1.57	0.120			
AI : aTPJ	-3.89(10.26)	-0.38	0.706			
Dx * AI : aTPJ	5.07 (14.73)	0.34	0.732			
Intercept	55.09(2.19)	25.08	0	0.124	4.55 (3,72)	0.0056
Dx	9.02(2.81)	3.21	0.002			
AI : pTPJ	-12.86(11.05)	-1.16	0.248			
Dx * AI : pTPJ	0.22 (15.66)	0.014	0.988			
Intercept	56.94(1.80)	31.61	0	0.143	5.19 (3,72)	0.003
Dx	9.43(2.59)	3.64	0.001			
AI : vmPFC	5.42(11.71)	0.46	0.645			
Dx * AI : vmPFC	12.68 (14.73)	0.86	0.392			
Intercept	60.69(3.06)	19.85	0	0.124	4.54 (3,72)	0.008
Dx	4.68(4.30)	1.09	0.281			
AI : rIFG	-23.81(14.95)	-1.59	0.116			
Dx * AI : rIFG	20.10 (19.96)	1.01	0.317			
Intercept	57.98(1.96)	29.63	0	0.254	9.52 (3,72)	0
Dx	8.32(2.53)	3.28	0.002			
aTPJ : pTPJ	-10.91(9.50)	-1.19	0.255			
Dx * aTPJ : pTPJ	-15.59 (11.79)	-1.32	0.191			
Intercept	54.47(2.39)	22.71	0	0.117	4.34 (3,72)	0.007
Dx	10.58(3.01)	3.51	0.001			
aTPJ : rIFG	-16.27(12.26)	-1.33	0.189			
Dx * aTPJ : rIFG	21.21 (14.97)	1.42	0.161			
Intercept	54.58(2.55)	21.41	0	0.124	4.53 (3,72)	0.006
Dx	8.67(3.29)	2.64	0.010			
aTPJ : vmPFC	12.48(11.19)	1.12	0.268			
Dx * aTPJ : vmPFC	-2.36 (14.15)	-0.17	0.868			
Intercept	56.84 (1.78)	31.86	0	0.103	3.87 (3,72)	0.0126
Dx	7.26 (2.56)	2.83	0.006			
pTPJ : vmPFC	-5.58 (11.97)	-0.47	0.642			
Dx * pTPJ : vmPFC	14.13 (15.91)	0.88	0.378			
Intercept	56.84 (1.78)	31.86	0	0.103	3.87 (3,72)	0.0126
Dx	7.26 (2.56)	2.83	0.006			
pTPJ : rIFG	-5.58 (11.97)	-0.47	0.642			
Dx * pTPJ : rIFG	14.13 (15.91)	0.88	0.378			
Intercept	56.37 (1.76)	32.04	0	0.109	4.06 (3,72)	0.01
Dx	8.31 (2.46)	3.38	0.001			
vmPFC : rIFG	-9.98 (8.57)	-1.17	0.248			
Dx * vmPFC : rIFG	10.84 (12.40)	0.87	0.385			

CHAPTER 5

Conclusion and Future Directions

5.1 Conclusion

The social relevance of empathy to help us understand, communicate, and interact with others effectively has been conceptually understood for a long time. Yet, contemporary research seeking to quantify and identify atypical qualities of empathy that are clinically relevant has been largely stalled by differences in operational definitions and methodology (Hall and Schwartz, 2019). Philosophy research has largely emphasized the importance of empathy for morality and cultural advancements, psycho-social accounts have focused on the developmental implications of empathy, and more recently, cognitive neuroscience has increased our understanding of the neurobiological basis for how we come to engage empathy in our day-day lives. Recent studies seeking to find better agreement across these disciplines point to an evolutionary advantage of autonomic nervous systems in group-living animals that are sensitive to the behaviors of others for basic survival and social well-being (Howe, 2012; Singer and Lamm, 2009).

Towards a more unified understanding of empathy components that could serve as practical intervention targets, advancements in implicit and explicit methods have encouraged the use of more holistic approaches for investigating the interplay between brain and behavior. Thus, as our understanding of the empathic experience reaches new depths, we can begin to disentangle various components of empathy that are affected in clinical populations. In autism, empathy is related to social and communication symptomatology. Social symptoms like the ability to establish and maintain relationships rely on cognitive skills like an ability to infer the intentions of others towards themselves and equally important, towards other social partners. Communication symptoms include the use of non-verbal cues like facial expressions and body gestures to transmit social intentions to social partners. These separate but related processes are subserved by specific brain networks whose connections are shaped by experience and development.

One overarching goal for the present study was to generate a unified hypothesis and characterization of empathy differences in autism that leveraged findings from separate lines of research. A clearer, more integrated understanding began to emerge as studies began to approach the empathy problem using a biopsychosocial framework. Better agreement in operationalized definitions of empathy that consider the individual contributions of affective and cognitive components certainly helped this effort along. Yet, as more and more studies began adopting this dual framework, empathy research in autism was challenged by disagreement in reports of intact (Dziobek et al., 2008) and dampened emotional empathy (Gu et al., 2015; Mul et al., 2018).

My own literature review suggested that discrepancies were likely attributable to varied methods using implicit physiological versus explicit self-report indices of emotional empathy. Separately, theoretical models on the hedonic properties of empathy began to emerge (Williams, 1990), but few autism studies explored empathy as a valence-dependent construct (Ashwin et al., 2007; Mazza et al., 2014). Finally, evidence for atypical neural responses in autism was largely limited to empathy for pain studies using in-scanner tasks that can be challenging and of low utility for use with individuals with significant autism symptoms (Fan et al., 2013; Lassalle et al., 2018). Together, these limitations presented critical gaps in our understanding of empathic behavior and brain function across the autism spectrum.

The present study sought to address these limitations using a single task, the Multifaceted Empathy Test-Juvenile (MET-J; Dziobek et al. 2008), and a single large cohort of a broad age range. Together, the methods we have employed across all three projects better capture the multidimensional nature of empathy and how its various components differ in autism. The MET survey results presented in chapter 2 support reports of global cognitive empathy challenges in autism and provide new valence-specific insights regarding emotional empathy. We found a valence by diagnostic group effect in emotional empathy of greater contrast when resonating to positive versus negative stimuli in our neurotypical development group that was not as distinguishable in our autism group. We also found a significant valence by age group interaction when predicting self-report arousal ratings indicating that relative to negative facial expression images, positive facial expressions elicited greater arousal in children and adolescents but not in our adult groups.

Our study of spontaneous facial expression production (FEP) in response to images of emotionally charged negative and positive facial expressions provided implicit empathy insights. While we expected to find atypical FEP in autism, we did not expect to find that high variability was not autism specific. After accounting for inter-individual variability in both groups, we found that over FEP was still significantly higher in our autism group compared to our neurotypical development group. Subsequent exploratory correlation analysis revealed that high expression was related to lower emotion recognition accuracy in autism but higher emotion recognition accuracy in neurotypical controls. Finally, we have shown that task-dependent functional connectivity differences found in autism among empathy regions are also present at rest. The following sections will discuss these findings in relation to current research.

The findings discussed in Chapter II challenge the traditional claim that autism is characterized by an empathy deficit (Kanner, 1943; Baron-Cohen et al., 1985). The work presented here does not support such an overgeneralization. Instead, we have shown that emotional empathy, an affective component, is intact in autism and that a more nuanced picture emerges when considering the valence of the experience. The valence of emotionally charged facial expressions did not differentiate the degree of emotional resonance in autism as much it did in our neurotypical controls. In autism, emotional resonance was similar in response to both positive and negative facial expressions, while for controls, there was less resonance with negative than with positive expressions. The adaptive implications of this are twofold. First: relatively stronger emotional resonance in autism to negative scenarios may lead to behaviors that impede social connection and thus have negative social consequences. Second: unregulated emotional resonance in negative contexts could lead to challenging mental health burdens. In fact, studies investigating the role of emotion regulation on social, mental, and physical outcomes suggest that there is a positive relationship between emotion dysregulation and negative outcomes across these three characteristic domains of autism symptomatology (Cai et al., 2018).

Regarding cognitive empathy, we found that emotion recognition capabilities are challenged in autism regardless of whether the observed emotions were of positive or negative valence. This finding is in line with theory of mind studies in autism and suggests that autism is more broadly affected by increasingly complex socio-cognitive demands. We also report age effects indicating that children in our neurotypical development (ND) and autism groups displayed significantly lower emotion recognition accuracy than adults. Recognizing discrete emotions from faces is characteristic skill and feature of neurotypical development (Bornstein and Arterberry, 2003) that is continually refined with perceptual learning and helps communicating complex emotional states (Pollak et al., 2009). In line with this, we found that performance on the CE task increased with age throughout childhood, reaching an asymptote at approximately age 18–20. To this point, Schulte-Rüther and colleagues suggest that autistic adults develop compensatory mechanisms to meet empathic demands of emotional resonance and emotion recognition (Schulte-Rüther et al., 2010). They report age-dependent decreases in neural recruitment of empathy network regions in neurotypical controls that coincided with either increasing or unchanged age-dependent neural recruitment in autism (Schulte-Rüther et al., 2014). These findings point to a potential sensitive period during which neurodevelopmental changes important for emotion recognition typically occur and a potential age window for targeting empathy skill training.

We were also interested in exploring the relationship between emotion recognition and spontaneous FEP. Based on facial expression autism studies' suggestion that autistic facial expressions are atypical in appearance (Trevisan et al., 2018), we expected that unsupervised machine learning methods like k-means clustering would differentiate our neurotypical and autistic adults based on overall FEP. Instead, we found that the k-means approach better differentiated each diagnostic group into a larger, less variable subgroup and a smaller, more variable subgroup. The larger subgroups were characterized by lower overall FEP and greater congruency between expressed and observed emotions while the smaller subgroups exhibited greater FEP but lower congruency between the observed and expressed emotion.

These findings are of import regarding their comparative value in that the presence of smaller more expressive, more variable, and less congruent groups in both our ND and autism samples suggests that exaggerated expressivity is not an autism-specific feature. Yet, there was still greater facial expression production in autism even after controlling for inter-individual variability. This was an unexpected result given that previous reports do not suggest that facial expression intensity is affected in autism (Keating and Cook, 2021) despite prevalent clinical descriptions of both "flat affect" (Capps et al., 1993; Stagg et al., 2014) and "exaggerated" expressions (Faso et al., 2015; Wozniak et al., 2017). Yet the presence of this subtle difference of greater overall expressivity could lead to negative evaluations from peers and reduce the overall quality of social interactions (Stichter et al., 2010). Further, facial expression production and reciprocity are important for socio-emotional constructs like emotional regulation Gross and John (2003) and the success of social interactions (Halberstadt et al., 2001).

5.1.1 A Unified Hypothesis to the Empathy Problem in Autism

The collective findings of the present study highlight and support the importance of self-other distinction as an integral capacity for the experience of empathy. Relatively less self-reported emotional resonance to negative stimuli in controls may reflect better self-other distinction in negative contexts compared to autistic individuals. We further show that this advantage persists across development. We have shown that task-dependent neural substrates of empathy are represented in intrinsic functional connectivity among empathy network regions. We also preliminarily identified two regions important for self-other distinction in social contexts that when coupled with the amygdala are related to better emotion recognition in autism but not neurotypical controls. In line with findings from Schulte-Rüther et al. (2010, 2014), this points to a potential compensatory mechanism to emotion recognition in autism that relies on the self-experienced emotion in response to others. In the process of making sense of the self-experienced emotion, it is possible that autistics rely on implicit sensory feedback from facial expressions more than neurotypical controls which would explain the overall increase in expressivity and lower emotion recognition when the felt and observed emotions do not match.

5.1.2 The Double Empathy Problem

The comparative work discussed thus far comes from studies attempting to explain and characterize autism as a deviance from normal development and cognitive functioning. This long standing case-control design and framework has recently been challenged by critiques on the use of neurotypical people as a "normal" reference point and suggest that social challenges between neurotypical and autistic individuals reflect a more reciprocal, double empathy problem (Milton, 2012). For example, findings of diminished social-cognitive differences when autistic individuals are partnered with one another, suggest that reports of empathy deficits should be reframed as features specific to interactions rather than the individuals themselves (Edey et al., 2016; Morrison et al., 2020).

In the context of the present study, we are limited to one half of the empathy problem as we explore autistic responses to static stimuli depicting neurotypical facial expressions. A more precise characterization of empathy in autism would explore the same concepts presented in this study using images from autistic individuals in equally emotionally charged scenarios. This approach would also provide helpful insights and a more balanced understanding on the empathy experience of neurotypicals towards autistic individuals. Further, as the empirical evidence supporting a more dimensional conceptualizing of autism grows, studies should favor the use of stimuli that is more representative and neurodiverse inclusive (Sonuga-Barke and Thapar, 2021).

5.1.3 Summary of Future Directions

This study opens exciting avenues for future research. Primarily, we are interested in complementing our sensory feedback hypothesis of increased facial expression production in autism as a mechanism for emotion recognition by testing for sensory threshold differences in face. The basis for this curiosity stems from empirical reports that the ability to recognize and understand people's faces is challenged by clinical and experimental disturbances to sensorimotor processing in the face like facial paralysis and mechanical blocking, respectively (Wood et al., 2016).

Separately, a big limitation of task-based studies in autism is that any findings speak only to higher functioning autistics that meet a full-scale IQ score of 70 or higher. This exclusionary criterion is typically put in place to ensure that participants understand their rights as research participants and that they can meet the cognitive demands associated with the tasks to be completed. However, our work using resting state functional connectivity suggests that this method would make a favorable alternative for interrogating brain networks in lower functioning autistic populations.

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