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Brain-Behavior Connections Underlying Emotion and Theory of Mind In Autism Spectrum Disorder

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Brain-Behavior Connections Underlying Emotion and Theory of Mind In Autism Spectrum Disorder

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Abstract

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that affects nearly 1 in 54 children. Children with ASD struggle with social, communication, and behavioral challenges due to deficits in theory of mind (ToM). In addition, diagnosis of ASD is complicated and there is an urgent need to identify ASD-associated biomarkers and features to help automate diagnostics and develop predictive ASD models. In this study, we conducted two experiments collecting behavioral and neuroimaging data from 9 children with ASD and 19 neurotypical children (NT) between the age of 7 and 14 years.

The first experiment examined specific elements of emotion recognition to better understand those skills needed for meaningful social interaction among children with ASD. Two previously tested measures of ToM, the Theory of Mind Inventory-2 (ToMI-2) and the Theory of Mind Task Battery (ToMTB), were used to evaluate early developing, basic, and advanced theory of mind skills impacting children's social skills. We also created and implemented two novel fMRI paradigms to probe the neural mechanisms underlying ToM related desire-based emotion and more complex emotions (i.e., surprise and embarrassment), as well as two early-developing emotions (i.e., happy and sad). Results suggested impaired abilities in multiple ToM metrics and brain deficits associated with ToM-related emotion recognition and processing among children with ASD. Findings from this study established connections between behavior and brain activities surrounding ToM in ASD, which may assist the development of neuroanatomical diagnostic criteria and may provide new pathways for measuring intervention outcomes in special populations such as those with ASD.

The second experiment adopted a novel evolutionary algorithm, the conjunctive clause evolutionary algorithm (CCEA), to select features most significant for distinguishing individuals with and without ASD, accommodating datasets having a small number of samples with a large number of feature measurements. Potential biomarker candidates identified included brain volume, area, cortical thickness, and mean curvature in specific regions around the cingulate cortex, the frontal cortex, and the temporal-parietal junction, as well as behavioral features associated with theory of mind. A separate machine learning classifier (i.e., k-nearest neighbors algorithm) was used to validate the CCEA feature selection and then used for ASD prediction. Study findings demonstrated how machine learning tools might help to facilitate diagnostic and predictive models of ASD.

Citations

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I dedicate my dissertation work to my amazing family, friends and many kind acquaintances who have shared their life and career wisdom with me. A special feeling of gratitude to my loving parents. It is hard for me to put it into words how much they have sacrificed to help me become who I am and to get me where I am today. They have given me unconditional love, generous support, patience, and encouragement. They also raised me to be courageous, adventurous and fearless and to step out of my comfort-zone to achieve my goals. Most importantly, they always make sure I know no matter how difficult things can be, they are always behind me. They are my biggest cheerleaders and greatest motivation to keep moving forward!

I also dedicate this dissertation to my beloved dog, whom I adopted on September,14, 2016 from the Chittenden County Humane Society, Burlington, Vermont. Ever since, she has never left my side, brought me countless joy and warmth, and kept me sane throughout this journey.

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Chapter 1

Comprehensive Literature Review

Chapter one provides an overview of Autism Spectrum Disorder (ASD) including a definition of the disorder, and a discussion of prevalence and possible causes. It then addresses theory of mind (ToM) as a core deficit in the ASD population. The relevant behavioral and brain literature related to ToM emotions in ASD are also discussed. Finally, machine learning is explored as an automatic diagnostic system and predictive model for ASD. See Figure 1.1.

1.1 Definition and Prevalence

ASD is a lifelong neurodevelopmental disorder in which the symptoms of a child can vary from mild to severe. According to the 2016 report from the US Centers for Disease Control and Prevention (CDC), about 1 in every 54 individuals has ASD [58]. Individuals with ASD have difficulties in communicating and interacting with others; they may also exhibit impairments in language and intellectual abilities. As a lifelong neurodevelopmental disorder, independence and quality of life are often impaired [92].

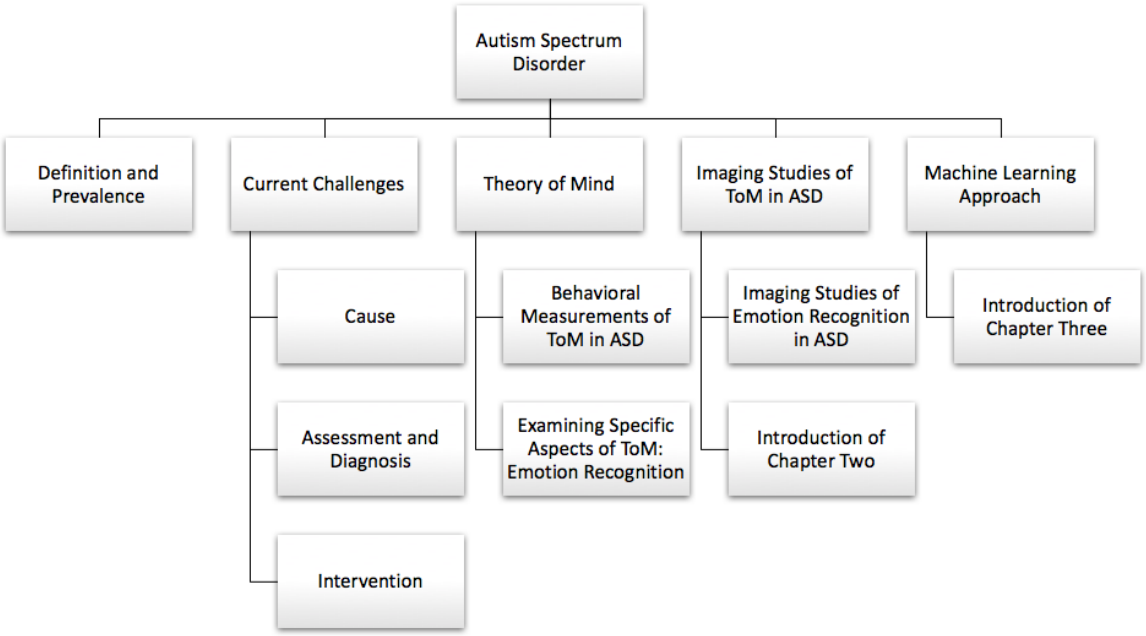

Figure 1.1: Chapter One Advanced Organizer

In the last several years, the prevalence and diagnostic criteria for ASD have changed in both epidemiological and clinical settings.

ASD was first described by Leo Kanner in 1943 [144] who found a new form of emotional disorder presented by 11 children. These children were able to engage in intellectual activities but had a strong desire to be left alone and rarely showed affection while interactions with others. In 1978, Rutter [233] described autism as a distinct syndrome that could be differentiated from other developmental disorders and outlined four criteria for diagnosis: onset before 30 months of age; impaired social development; delayed and aberrant language development; and insistence on uniformity, as shown by stereotyped play patterns, abnormal preoccupations, or resistance to change. The World Health Organization (WHO) included autism in the International Classification of Diseases (ICD-9) in 1975 [284]. The American Psychi-

atric Association included autism in the Diagnostic and Statistical Manual of Mental Disorders-III (DSM-III) in 1980 [8].

It was not until the 1980s that a less severe form of autism was found and identified as Asperger's syndrome and was eventually included in official nosographies in the 1990s, however, with no clear validity. People with Asperger's disorder tend to bear mild signs and symptoms of autism without language delays. Children with autism are often seen as aloof and uninterested in others. However, individuals with Asperger's disorder do not carry the same character as individuals with more severe autism [17]. Individuals with Asperger's disorder want to fit in a social group and engage in interaction with others in most scenarios, although they struggle with finding the appropriate approach. They can be perceived as being socially awkward while breaking conventional social rules or showing certain levels of apathy. Their interests in a particular subject tend to be obsessive. Individuals with Asperger's disorder typically do not have deficits in their language skills, however, they use language in ways that are different from others. Specifically, their speech patterns can appear to be unusual with a lack of inflection and excessive formality. They also have difficulty understanding the subtleties of language including irony, sarcasm and humor, or the give-and-take nature of a conversation [17]. Cognitively, a person with Asperger's disorder has an average to above-average intelligence [17]. Notably, the DSM-5 no longer has Asperger disorder as an independent disorder but instead considers it as part of ASD. It is an effort to eliminate distinctions that were made idiosyncratically and unreliably across different diagnostic centers and clinicians.

With several advances in science over the past 10 years, attention to the clinical, financial and social needs of those with ASD has increased. Significant challenges

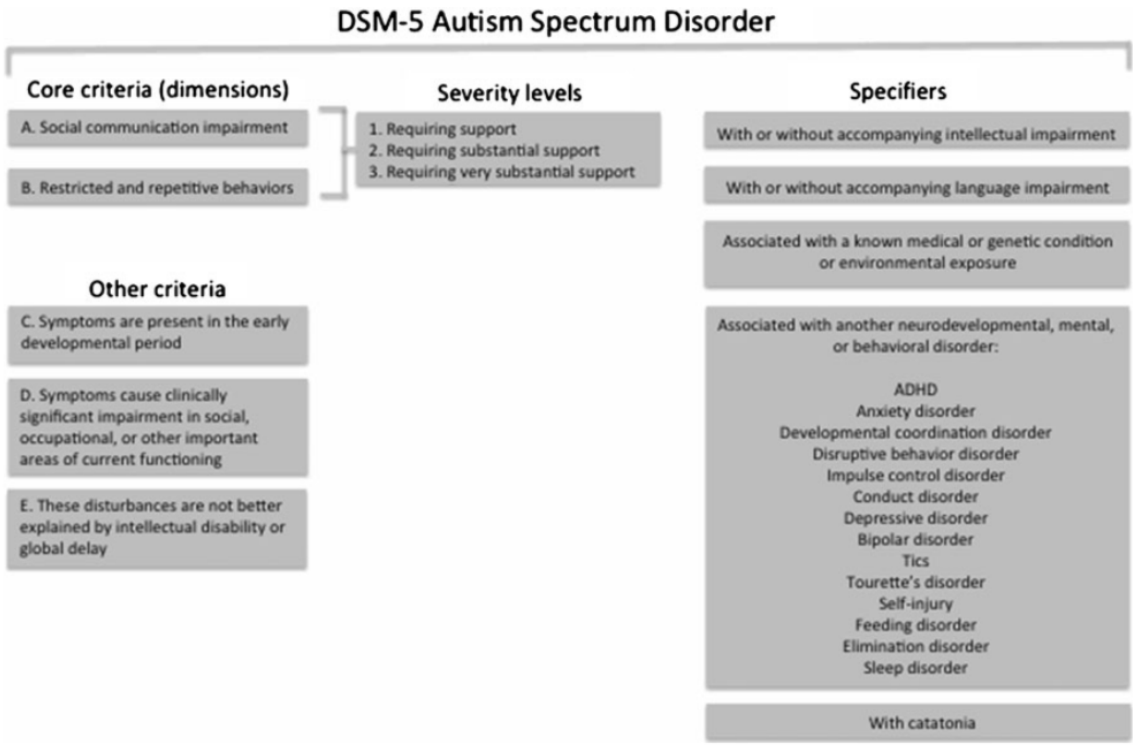

Figure 1.2: DSM-5 ASD Diagnostic Criteria and Specifiers. [207]

remain, however, in our understanding of etiology and effective treatment. Currently, the two major worldwide nosographies are the ICD-10 [285] and the DSM-5 [9]. See Figure 1.2 for specific diagnostic criteria and specifiers.

1.2 Current Challenges

There are four major challenges facing those that are affected by ASD:

- There is no identified cause of ASD.
- Access to clinical assessments with ASD specialists varies and procedures for diagnosis are tedious.

- There are high social and economic burdens for family and society.
- There are either limited resources or a lack of information to guide patients to choose appropriate intervention methods.

1.2.1 Cause

There is no definitive answer to what causes ASD or the range of severity that characterizes the disorder. Most clinical researchers would agree there are both environmental and genetic factors to consider. In fact, more than 100 genes are known to be risk factors [230] and about 1,000 genes (e.g., Pten gene [51,52,220]) have been associated with ASD [113]. Debate between whether genetic effects outweigh the environmental factors is ongoing. For example, one twin study suggested that shared environmental factors contribute to about more than 50% of the etiology for autism, with 37% is potentially led by genetic heritability [264]. However, other twin studies suggest that strong genetic effects play a significant role in the development of ASD such that concordance for monozygotic twins is roughly 45% while concordance for dizygotic twins is 16% [42]. Given the inconclusive and inconsistent results across twin studies, the exact role of genetic and environmental factors in ASD is ambiguous. It is possible that genes and the environment both influence the occurrence of ASD, such that certain environmental exposures combined with particular genetic predisposition can potentially lead to ASD [71, 226].

A few specific environmental factors have been identified to interact with genes in ASD. Maternal infection is a primary concern that can often be linked to ASD, in which naturally occurring pathogen exposure often provides the strongest evidence

for environmental etiology [82,172]. Although the maternal rubella (German measles) epidemic no longer exists, it was widely spread globally before the dissemination of effective vaccines. Between 1963 to 1965, 10,000 to 30,000 infants whose mothers were exposed to rubella were born with moderate to severe neurodevelopmental disorders, in which 741 per 10,000 were found to have autism [82, 172]. Another common and most prevalent infection is influenza. A series of animal research studies has associated prenatal exposure with influenza during fetal life with an increased risk of autism [209, 245]. Patterson and Shi [209, 245] suggest that the influenza virus activates the immune system of the pregnant woman, which is potentially harmful to fetal brain development. However, there is a lack of evidence suggesting the use of antibiotics and vaccines of influenza can cause ASD. Noticeably, nearly 64% of US women have had an infection during their pregnancies, and the newborns of these mothers did not develop ASD in most cases [64]. In summary, mild infection during pregnancy can increase the risk of a fetus for developing autism, but little evidence suggests that viruses are directly associated with ASD [287].

Autoimmune diseases is a disease in which immune cells attack other cells that are mistaken as "foreign". This process is mediated by circulating antibodies. Autoimmune disease currently affects as much as 9% of the world's population [6, 65]. Twelve percent of mothers of children with ASD carry unusual antibodies directed at fetal brain proteins. It indicates that circulating antibodies may lead to some forms of autism [46]. It is suggested that Maternal Antibody-Related (MAR) causes can be associated with to as many as 22% of autism cases according to the specific assays for these antibodies. It demonstrated a strong possibility that such form of ASD can potentially be prevented [101]. These studies have led a new direction to discover

potential therapeutic targets for ASD. There are still many challenges remaining to answer questions such as how antibodies enter the fetal brain and how that could alter the neurodevelopmental processes. However, there is no evidence arguing against the possibility of the circulating antibodies being a prenatal environmental risk factors for ASD.

Another important environmental factor is drug use during pregnancy. In the 1960s, there was evidence showing the association between the use of thalidomide, a sedative drug that was prescribed for relief of nausea during pregnancy, and the increased risk of autism in newborns [142]. More recently, there have been increased concerns surrounding the use of valproic acid and serotonin reuptake inhibitors (SSRIs) which are prescribed to treat epilepsy, migraine headaches, bipolar disorder, and depression during pregnancy [151]. To date, the largest epidemiological study included 415 children, among which 201 were born to mothers who took antiepileptic medication during their pregnancies. Nearly 7.5% of the children of those mother who took the medications developed a neurodevelopmental disorder, especially autism, comparing to 1.9% in the non-epileptic women [49]. Serotonin is an important brain neurotransmitter that plays a significant role regulating sleep, mood and appetite. Dysregulation of serotonin during early fetal life can lead to serious negative consequences for brain development [6]. The name, SSRIS, have been used since late 1980s. It delays the reuptake of serotonin from the synaptic cleft into the presynaptic terminal to enhance its effect on the postsynaptic receptors [6, 167]. A recent review and meta-analysis of six case-controlled studies and four cohort studies have found that SSRI use during pregnancy can be greatly linked to an increased risk of ASD in offspring, especially during the first and second trimesters of pregnancy [289]. Inter-

estingly, other studies linked the preconceptual exposure to SSRIs to increased ASD risks, which was the same case as to use of non-SSRI antidepressants. Specifically, although there was significantly more ASD cases in the SSRI-exposed (experimental) group comparing to the control group, if a mother already had a existing unmedicated psychiatric disorder or had discontinued the medication, the chances of their newborns developing ASD were as much as those mothers who had been exposed to SSRIs [145, 167]. It is noted that it is nearly impossible to remove the SSRIs if they are the needed drugs for a maternal condition. To summarize, a brief review of the literature has shown that the intake of some drugs during pregnancy [145] increases the risk of ASD. Thus, use of drug during pregnancy and fetal development needs to be evaluated carefully. Mothers need to consider all potential risky outcomes before taking a drug for widespread medical purposes.

Environmental toxins, such as air pollution produced by automobiles and cigarettes, heavy metals, and pesticides are also considered potential risk factors for autism [182, 206], although with little evidence for this. One historical concern is vaccines, such as the measles, mumps, and rubella (MMR) vaccine. These vaccines are typically administered initially when the child is 12 to 18 months old, which can become high risk factors of developing ASD for a healthy child [222]. This fear was sustained by regressive onset in some cases. Specifically, a child may start to show social and language deficits after the first year and slowly develop autistic characteristics. However, research suggests that even in children who display this regressive form of autism, brain changes happen long before behavior changes, typically around four to six months. Furthermore, there is no evidence showing a relationship between MMR administration and the development of ASD. The author who published data

suggesting increased risk of ASD with MMR administration faced significant public shaming. These findings from many large-scale epidemiologic studies are consistent with the conclusion that the US National Academy of Sciences reached in a thorough review carried out in 2011 [76, 200].

Overall, many theories exist about how one develops autism, but these possible risk factors still remain mysterious as there is no direct and established conclusion for a single causal factor.

1.2.2 Assessment and Diagnosis

Currently, the diagnosis of autism is solely based on behavioral symptoms. A typical diagnostic appointment includes a multi-hour behavioral evaluation by a team of clinicians. Diagnostic appointment usually happens in a specialized diagnostic clinic or developmental medicine center. In many cases, such appointment can only be made after a referral from the child's general pediatrician. During diagnostic appointments, clinicians and interventionist deliver a series of behavioral assessments with different rating scales. There are standardized schemes regarding the evaluations derived from the rating scales for clinicians to follow in order to reach a best-estimate diagnosis [168]. There are two gold standard behavioral assessment tools guiding the diagnostic process, *The Autism Diagnostic Observation Schedule-second edition (ADOS-2)* and *The Autism Diagnostic Interview-revised (ADI-R)* [173, 174]. The ADOS-2 is considered the gold standard for assessment of ASD. It is an observation-based clinical assessment that is broken into five modules based on age and language level: "the toddler module is for children between 12 and 30 months of age who do not consistently use phrase speech, module 1 is intended for young children with no

or single-word speech, module 2 is intended for individuals with phrase speech, module 3 is intended for verbally fluent children, module 4 is intended for verbally fluent adolescents and adults" (Levy et al., 2017, p.4) [168]. During the ADOS assessment, the administrator engages in series of standardized activities with the child and answers a set of questions based on his/her observations of the child's behavior. The total time for administration and scoring of the ADOS is approximately 60 min. The process of ASD diagnostic examinations is time-consuming due to its rigorous nature. Because of that, many diagnostic centers have a long waiting list as the capacity of available clinicians is extremely limited. In addition, those using the ADOS-2 must complete a multi-day training to administer the assessment. This bottleneck directly leads to delays in diagnosis of 13 months and longer for minority and lower socioeconomic status groups. These delays can also delay insurance coverage and access to behavioral therapies [20, 180, 181, 225].

1.2.3 Intervention

Both biological and social cognitive intervention methods are available to help manage ASD-related symptoms and improve an individual's social communication skills. Psychosocial therapies such as applied behavior analysis (ABA), pivotal response treatment (PRT), and cognitive behavior therapy (CBT) have been commonly used to treat ASD and elicit positive effects to improve learning and verbal communication and ease ASD-associated symptoms such as anxiety [75].

In 2009 and then again in 2015, The National Autism Center (NAC) reviewed hundreds of interventions used to address the symptoms of autism described in peer-reviewed scientific journals, and described 11 established interventions (NAC, 2009)

which expanded to 14 (NAC, 2015) based on the available research for children, adolescents, and young adults (under 22 years of age) with ASD [16]. Four factors were adopted to help select appropriate and effective intervention methods: evidence of intervention effectiveness, professional judgment, data-based clinical decision making, values and preferences of families including the individual on the autism spectrum, and capacity to accurately implement an intervention. The 14 established interventions identified in 2015 include behavioral interventions, cognitive behavioral intervention package, comprehensive behavioral treatment for young children, language training and production, modeling, natural teaching strategies, parent training, peer training package, pivotal response training, schedules, scripting, self-management, social skills package, and story-based intervention. For individuals who are 22 years and older, behavioral interventions is the only recommended intervention [16]. Most of these interventions come from the behavioral literature, including ABA, behavioral psychology, and positive behavior supports. It is important to know that most of the intervention methods benefited from a broad range of expertise and knowledge in fields such as developmental psychology, special education, and speech-language pathology.

Caregivers of individuals with ASD often face more stress than those who deal with other disabilities, which contributes to challenges in their own relationships and mental and physical health conditions. Caregivers are required to commit a tremendous amount of time, effort and patience to meet the high care demands of individuals with ASD. Moreover, many parents of children with ASD suffer with financial challenges, especially with the high out-of-pocket health care expenses, underemployment, or employment loss [114, 150, 157, 158]. Not surprisingly, these parents often feel the strain

of caregiving and are at risk for mental health challenges such as anxiety and depression [114, 150]. At a societal level, Leigh and Du [165] revealed that the economic burden of the ASD population in 2015 was around $268.3 billion and in 2025 will be $460.8 billion, representing 1.5 and 1.6 %, respectively, of GDP. These estimates range from $161.6 billion (0.9 % of GDP) to $367.3 billion (2.0 % of GDP) in 2015 and from $275.6 billion (1.0 % of GDP) to $1,010.6 billion (3.6 % of GDP) in 2025. These estimates are based on the increased number of ASD individuals, the expenditures on medical care and non-medical care, and the lost productivity for parents and their children with ASD [165]. Given the hardship at both family and society levels, it is essential to find appropriate and efficient methods to diagnose ASD and manage symptoms, particularly the significant social impairment which differentiates ASD from other neurodevelopmental disorders.

1.3 Theory of Mind

Among all of the deficits identified for children with ASD, their social impairment is primary and interferes with many aspects of their development. Many believe that at the core of this social impairment is a deficit in theory of mind (ToM) [21, 23]. ToM is the ability to reason about the thoughts and feelings of self and others, including the ability to predict what others will do or how they will feel in a given situation on the basis of their inferred beliefs [21, 23]. ASD individuals have trouble interpreting or reading the verbal and non-verbal social communication of other individuals in a way that accords with normative expectations [9]. It has been argued that individuals often encounter difficulties interacting with others appropriately within a social

context when their abilities to interpret the beliefs, intentions, and emotions of others are impaired [48, 126].

There are three major components of ToM [53]. The first one is *shared world knowledge*, such that ToM is always situated in the context of the surrounding world. For example, an individual must be able to infer their partners' thoughts, beliefs, emotions, and goals during a typical conversation to respond properly. The individual also needs to be able to integrate cues from their surroundings during interactions with conversational partners, "such as prior world knowledge (e.g., amount of personal space the conversational partner needs to feel comfortable), knowledge about the relationship between individuals (e.g., how much is an appropriate amount of disclosure with a close friend vs. a co-worker), the goal of the conversation (e.g., what information is required to exchange between the two individuals), and the condition where the conversation occurs (e.g., in a group setting or a private room)" (Byom and Mutlu, 2013, p.2) [53, 153, 238]. The second component of ToM is *the perception of various social cues*, such as gaze, facial expressions, and vocal cues. Gaze is a major cue of the direction of one's attention and people often follow one's gaze to determine the partner's intention. Gaze also helps an individual track the understanding of one's message as well as to send feedback [29, 30, 103, 149]. Like gaze, emotion recognition is a crucial ability to infer mental states. The ability to discriminate between different facial expressions is typically generated in childhood and continues to develop into adulthood with both children and adults more accurately identifying positive emotions (e.g., happy) than negative emotions (e.g., sad) [185, 249].

The last component of ToM is *interpretation of actions*, such that humans believe that others act in ways that are consistent with their beliefs and goals. People

are able to understand other's intentions and beliefs by passively observing their actions [4, 282]. Many studies have demonstrated correlations between ToM and circumscribed aspects of NT children's everyday behavior including social pretend playing and secret-keeping, aggression and bullying, and reciprocated friendship [95, 137, 212, 224, 253, 257]. More importantly, however, such relations are limited and have not emerged as clearly in the domain of generalized social skills. Instead, studies have either found no significant associations at all between social skills and false belief understanding in NT children, or mixed results indicating no relationship between social behaviors and ToM development [79]. A recent study, however, showed a strong correlation between peer interaction surrounding leadership and group entry and ToM understanding among NT and deaf children, but such a correlation did not exist in the ASD group. The apparent link of ToM to peer competence in ASD was instead greatly mediated by language ability [213].

ToM deficits supposedly underlie social communication impairments in ASD [25, 119, 254]. ToM has also demonstrated potential as a severity index in ASD. That means that better ToM is associated with improved behavior towards social rules [262], better social interaction skills [41, 100] and increased language use [60, 116]. ToM is particularly useful in discriminating the level of support needed in "high-functioning" ASD children. Besides levels of intelligence quotient (IQ), cognitive modifiability, executive functioning, and central coherence, studies that examine potential cognitive indicators in terms of level of special support needed have found that ToM is the only cognitive indicator to predict school placement. ToM successfully differentiated between children who need support and those who do not [5]. Behavioral and social competencies strongly predict children's ability to successfully integrate

into public education system [141, 177, 286].

1.3.1 Behavioral Measurements of ToM in ASD

Many instruments have been developed to measure ToM in ASD [48]; however, there has not been any universally accepted operationalization of ToM. Research in the old days were mostly shaped by studies examining ToM in young NT children. These studies often used a variety of different false belief tasks in primary developmental research [19, 43, 282]. Findings from these older studies showed that many older children and adolescents with ASD could pass such common tests regardless of their pronounced social impairments associated with ToM deficits. Thus, researchers developed more age-appropriate tests that can accurately measure the social-cognitive deficits among older individuals. For example, *The Reading the Mind in the Eyes Test* examines the person's ability to link a specific mental state descriptor (e.g., flirtatious, hostile) to the expression demonstrated by an image of a pair of eyes [26]. Another test, *the Strange Stories* [117] task includes a number of scenarios or stories that are presented on paper. In this task, the examinee is required to explain the purpose of the behavior of the key characters within the scenarios. In these scenarios, the characters use expressions that have meanings that are different from what a literal interpretation of the expression might indicate (e.g., metaphors, sarcasm, white lies). There were mental or social stories (i.e., stories requiring a reading of the social intent of the characters) and control stories (i.e., stories not requiring any social inferences) in Happe's original instrument. When comparing to the IQ-matched controls, individuals with ASD were expected to perform worse on the mental or social, but not the control (i.e., physical) stories. Subsets of items from the *Strange Stories*

test [99, 118] have provided the stimuli for many other examinations of ToM deficits in both children and adults with ASD.

Nearly all behavioral tests of ToM currently available only examine one or a few aspects of ToM; however, two measurement tools *The Theory of Mind Inventory-2 (ToMI-2)* [131] and *The Theory of Mind Task Battery (ToMTB)* [134] are multi-faceted tools that cover several aspects of ToM (e.g., emotion recognition, false belief, perspective taking etc.), including information from both parent and child. The ToMI-2 measures a parent's perception of their child's ToM understanding of 60 items using a 20-unit rating scale from "Definitely Not" to "Definitely". Primary caregivers use a vertical hash mark to indicate where on the continuous scale best represents their perceptions. Item, subscale, and composite scores range from 0-20. A higher number indicates a parent's greater confidence in their child's understanding of a particular ToM skill. The ToMI-2 items represent typical social interactions to ensure it is a socially and ecologically valid ToM index. The tool demonstrates excellent test-retest reliability, internal consistency, and criterion-related validity for neurotypical children and children with ASD as well as contrasting-groups validity and statistical evidence of construct validity (i.e., factor analysis) [131, 133, 166]. The ToMTB is a direct measure of a child's understanding of ToM, see Figure 1.3. It consists of nine ToM tasks presented as short vignettes in a story-book format arranged in ascending difficulty. For each of the nine tasks, children are provided with one correct response option and three possible distracters. There are 15 total questions asked, including memory control questions that must be answered correctly to get credit for ToM understanding. The ToMTB has strong test-retest reliability [131, 134].

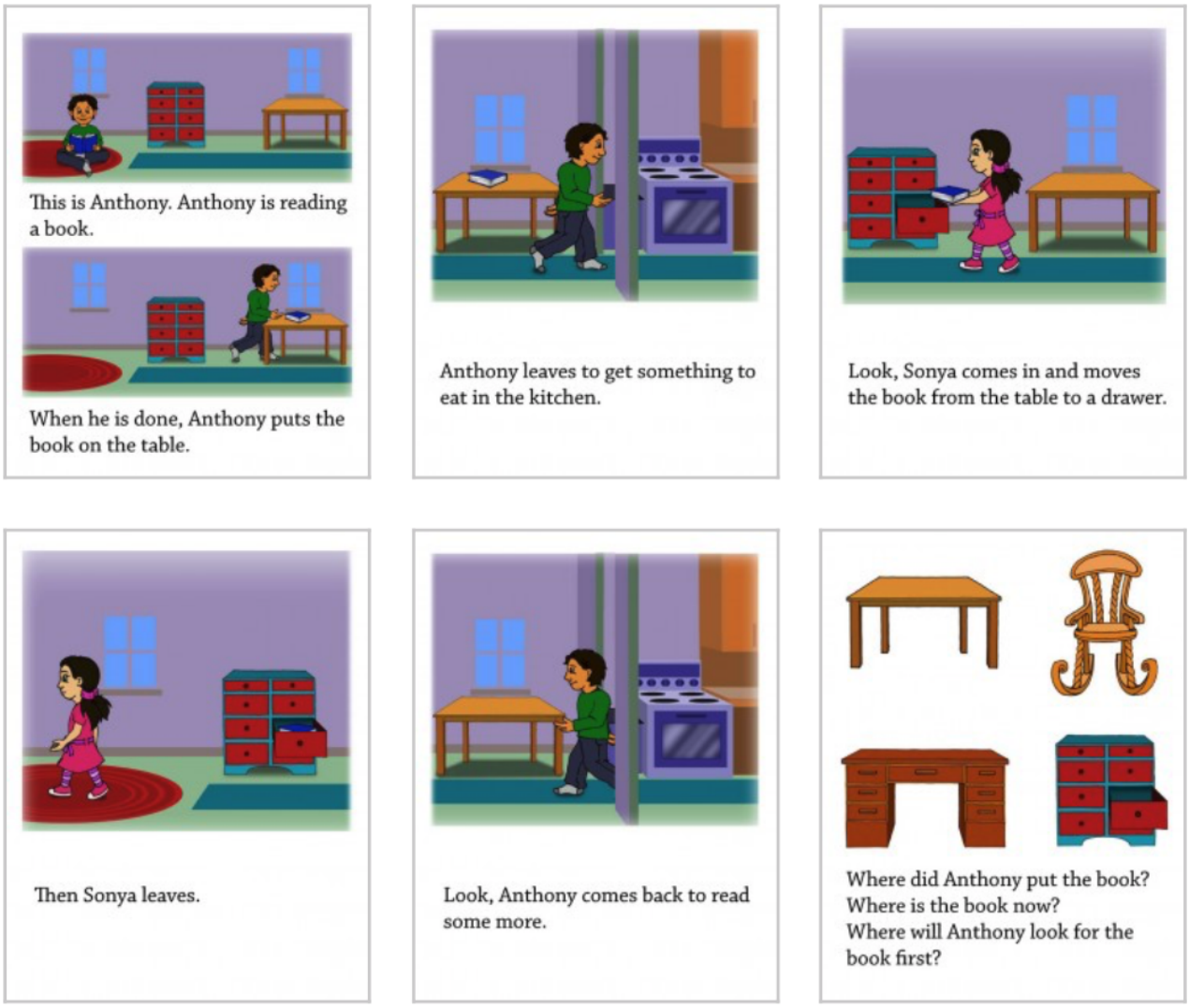

Figure 1.3: Examples from the Theory of Mind Task Battery. [131, 132]

1.3.2 Examining Specific Aspects of ToM: Emotion Recognition

Although ToM has been studied for decades, it still remains a challenging research area due to its multi-faceted composition. Further, few studies have investigated the neural mechanisms underlying ToM, especially among children. Thus, a greater understanding of the brain-behavior connections associated with ToM will provide researchers with a potential link between the biological mechanisms of ToM associated with the behavioral characteristics, leading to more efficient diagnostic processes and prognostic indicators for special populations like children with ASD. To facilitate increased understanding of this linkage, this study emphasized emotion recognition as one aspect of ToM with a specific focus on less well-studied and more complex emotions (i.e., surprise, embarrassment and desire-based emotion).

Emotion recognition is one particular aspect of ToM that has a critical role in an individual's ability to meaningfully engage in social communication and social interaction. It is the ability to discriminate between different facial expressions and is key to understanding empathy or the feelings of others. Children with ASD have impairments in social interaction often due to a lack of understanding of emotions and the minds of others, as well as difficulty attending to social cues (e.g., gaze, facial expressions, body postures etc.). Some studies have found that children with ASD use the lower part of the face to determine one's facial expression and often ignore or have difficulty identifying negative facial affect (e.g., distress, fear) evident near the eyes as early as the age of three [160]. However, other studies suggest that children with ASD have trouble recognizing emotions from the lower part of the face comparing to

NT children [160]. There is a wealth of behavioral evidence showing that recognition of even more "basic" emotions like happy and sad are impaired in individuals with ASD [10, 66, 72], with some emotions requiring greater ToM development than others (e.g., surprise, embarrassment, desire-based emotion).

Happy

Happiness is one of the first emotions neurotypical (NT) infants discriminate [40,132]. Mastery might occur because it is easily visible, biologically influenced or frequently observed [91, 251]. With the early awareness of happiness, it is described as an early developing ToM skill [132]. Further, it is the most frequently recognized emotion not only for NT children but for those with developmental disabilities [183]. In fact, research shows the recognition of happy expressions may be intact for those children with ASD who have higher cognitive and linguistic abilities [11, 132] and appears to be more intact than recognition of other emotions [70, 162, 232, 265, 271]. Notably, however, individuals with ASD may not be attuned to the social value of happiness which could impact their desire to engage with others [132, 161, 240].

Sad

Similar to the early recognition of "happy" or "happiness" in children, negative emotions such as "sad" also emerge early in development and can be distinguished by infants [94, 132, 268]. In contrast to the ease in the development of recognizing happiness in children with ASD, recognizing "sadness" is more challenging. There seems to be a disconnection for those with ASD in their ability to process and visually scan atypical faces, and since understanding "sadness" requires the ability to make sense of

the eye region of the face, their responsiveness is reduced [67,90,132,218,269]. Diminished ability to recognize sadness also appears to be related to more severe autistic symptoms and greater difficulty independently managing day to day activities such as personal care [121, 132].

Surprise

As a "cognitive" versus "basic" or early developing emotion, surprise requires an individual to understand the ways in which emotions are influenced by one's expectations or beliefs about something [132]. Understanding the emotion of surprise requires children "to understand that a person approaches a situation with a specific expectation in mind, and if the situation does not match that expectation, then the person will be surprised" (Lacroix et al., 2014, p. 1147) [162]. Surprise emerges later in development and not before preschool [24,83,108,112,132]. Knowing that understanding one's own and others' desires, beliefs and values is a particular area of deficit for children with ASD, it is not unexpected that they would experience difficulty making sense of "surprise". Difficulty in the recognition of surprise among children with ASD also appears to fall behind understanding false belief [178, 231]. It is an emotion induced by what someone thinks is the case, even if the reality does not match with what is actually on one's mind.

Embarrassment

Embarrassment is often described as a "self-conscious" emotion that is associated with a feeling of shame or awkwardness around some action or statement [56, 124, 125]. Experiencing "embarrassment" does suggest some level of self-awareness that an "ex-

pected" behavior in a social context was unmet [33, 86–88]. Children with ASD may show an emotional response of embarrassment, although to a lesser degree than their NT peers. Further, they seldom recognize embarrassment or express their experiences in situations of embarrassment [132]. Often, they miss social gaffes where what is said is perceived as an inappropriate comment in a social context. In addition, conditions that bring out embarrassment among children with ASD are often different from those described by NT children. For example, children with ASD often respond to embarrassment more strongly when they are embarrassed vs. when something they have done is embarrassing to others. Having a better understanding of embarrassment will ultimately allow children with ASD to better navigate the social world and interact with other people in more appropriate ways, following the expected social norms and expectations [77, 84, 132, 176, 239].

Desire-Based Emotion

Desire-based emotion recognizes the relationship between getting what you want and feeling happy and not getting what you want and feeling sad or disappointed [132,227, 228]. Thus, desire-based emotion can lead to positive emotions or negative emotions, depending on a fulfilled or unfulfilled desire. Importantly, research suggests that children with ASD are better able to navigate emotions at a basic level in support of previous research [14, 15, 55, 80, 98, 120, 132, 215]. Challenges remain, however, in understanding the vulnerability of desire-based emotions in children with ASD as they often are unable to generalize their understanding without explicit instruction and support in social contexts [132]. Desire-based emotion plays an important role when understanding and empathizing with others'thoughts and feelings [216, 229, 278].

1.4 Imaging Studies of ToM in ASD

Most studies have examined ToM through behavioral approaches, especially among the ASD population due to challenges associated with procedures such as staying still in a magnetic resonance imaging (MRI) scanner or wearing an electroencephalography (EEG) cap. Studies have established important roles of the medial prefrontal cortex (mPFC), posterior superior temporal sulcus (pSTS), and temporal parietal junction (TPJ) in processing ToM among both ASD and NT participants, with ASD subjects exhibiting decreased activation and connectivity in those regions, see Figure 1.4. Specifically, the mPFC is associated with mental state reflection; the pSTS is involved in inferring others' actions; and the TPJ helps with understanding beliefs and socially relevant information. It is suggested that there is an altered/reduced recruitment of the ToM network in ASD [143, 205, 256]. Brain activation in the ASD group is reduced in regions associated with processing ToM, including the superior frontal gyrus extending to the mPFC, angular gyrus extending to TPJ and pSTS, precuneus, and posterior cingulate cortex (PCC) [143, 205, 256]. Other studies have found reduced functional activation in the superior temporal sulcus, fusiform gyrus (FG), amygdala, mPFC, and putamen among ASD participants comparing to NT participants when recognizing and processing basic emotions such as happy and sad [136, 252, 255]. Abnormal levels of activation are found in ASD subjects involving the ToM network (e.g, mPFC and TPJ), the mirror neuron network (e.g., inferior paricta lobule, primary motor cortex, inferior frontal gyrus, superior temporal sulcus, and occipital lobe [221]), and the cerebellum using the Frith-Happe animation task that is aimed to assess ToM ability through attributed mental states to two triangles

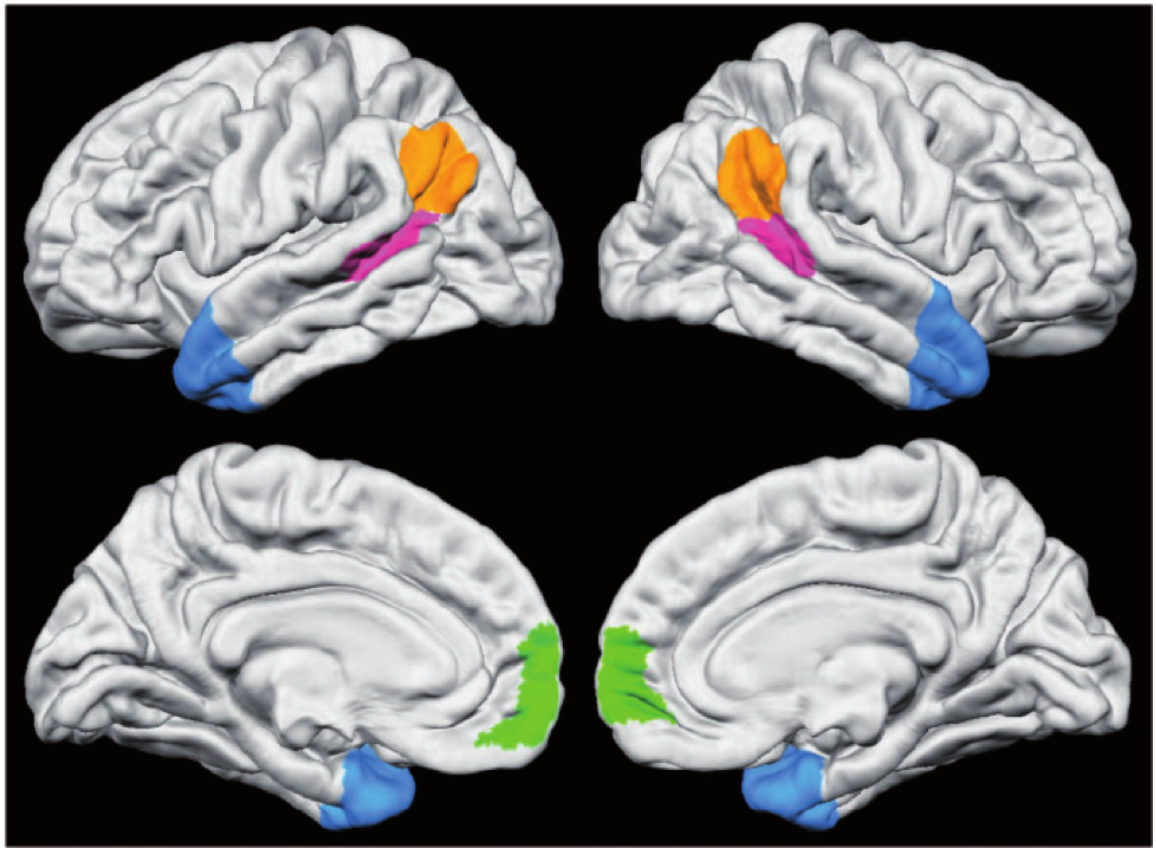

Figure 1.4: The Social Brain: mPFC (green), TPJ (orange), pSTS (pink). [187]

interacting with each other [2,116]. Further, the anterior cingulate cortex, mPFC, and left superior temporal gyrus show decreased activities when regulating ToM-related self-conscious emotions (e.g., embarrassment and guilt) in ASD subjects [136,252,255]. Although there have been studies examining less well-understood (i.e., desire-based emotions, surprise) and more complex (i.e., embarrassment) emotions, they are either conducted from a behavioral perspective or with adult populations. Studies involving the adult ASD population, however, have given us some direction regarding the neural mechanisms underlying emotions in ASD, yet we remain unclear whether children exhibit similar or different brain activity patterns or no.

1.4.1 Imaging Studies of Emotion Recognition in ASD

The neural mechanisms underlying interpretation of happy faces in ASD are well studied, with a few important brain regions identified. A particular region of the cortex, the FG, is known to be the special area for processing of facial features and emotions. One study recorded the face-sensitive ERP to neutral and emotional faces with a high-density EEG system. The study indicated impaired activity patterns in the area of FG among ASD subjects when processing happy faces [10]. fMRI studies have suggested that there are decreased brain activities in areas of the left medial frontal gyrus including the left superior and medial frontal gyri, right superior and medial frontal gyri, and the anterior cingulate gyri, the right and left temporal poles, left TPJ, left pSTS, dorsomedial prefrontal cortex, and right and left middle superior temporal sulcus when processing facial emotions [72]. Due to high variability across fMRI studies, other brain regions are also identified, but overall reduced brain activities when processing happy faces are observed in ASD groups [189, 250, 279]. Research also suggests the ASD population is more sensitive to sad faces [279]. When processing sad faces, the ASD group tends to show greater activation relative to the control group in the amygdala, ventromedial PFC, putamen, and striatum, and younger adolescents show greater activation than older adolescents [72,279]. However, research found decreased activities in mPFC among ASD groups when processing sad faces [72].

Embarrassment has been studied at a neural level only among adults with ASD, suggesting altered circuitry underlying mPFC, anterior cingulate cortex (ACC), in-

ferior frontal gyrus (IFG), TPJ/pSTS, PCC, and amygdala [87, 124, 136, 169, 255]; surprise and desire-based emotions have only been examined in ASD subjects at a behavioral level and little is known about their neural correlates. Thus, examining the neural correlates of these emotions requiring ToM and establishing the connections between behavior and brain activities in children with ASD is important. As mentioned earlier, there are no current identified biomarkers that are considered to be necessary and sufficient to indicate ASD. However, research suggests that there is a strong link between biological (e.g., genes and hormones) and neurological factors (e.g., abnormal brain connectivity and structures) and the development of ASD [36, 202, 211, 223].

Building upon findings from previous studies, this study aimed to provide a deeper and more systematic understanding of the brain-behavior connections associated with ToM, leading to increased understanding of the brain regions associated with ToM. It allowed us to identify those brain structures associated with deficits in specific aspects of ToM. With this knowledge, intervention research can then be developed that supports brain behavior connections leading to normalized social performance. Such brain behavior research might also help predict those brain behavior profiles of children most likely to benefit from specific ToM or social cognitive based interventions. This is important as causal modeling in ASD suggests that interventions need to be delivered at the cognitive level to bridge behavior with brain function [128].

1.4.2 Introduction of Chapter Two

Chapter 2 introduces a study in which behavioral and neuroimaging data for children with and without ASD were collected, specifically in areas of emotion recognition to understand which key skills are required for meaningful social interaction. The

study included 9 children with ASD and 19 neurotypical children (NT) between the age of 7 to 14 years old. The ToMI-2 and the ToMTB were adopted to evaluate children's ToM understanding important to their development of social skills. Two novel functional magnetic resonance imaging (fMRI) paradigms were implemented to probe the neural mechanisms underlying ToM related to desire-based emotion, and more advanced and complex emotions (i.e., surprise and embarrassment), as well as two early developing emotions (i.e., happy and sad). The results suggest impaired abilities in multiple ToM metrics and brain deficits associated with ToM related emotion recognition and processing among children with ASD. The study findings suggest future research directions in the field when working with special populations such as those with ASD.

1.5 Machine Learning Approach

With the ongoing challenges discussed earlier and growing awareness of ASD, there is a high demand for immediate access to diagnostic services. An automated ASD diagnostic approach might allow for early diagnosis of ASD and help to provide a map of high-risk populations [208]. Building an automatic diagnostic and predictive model of ASD is timely, with many studies adopting machine learning approaches to identify sets of significant biomarkers including both behavioral and biological aspects. [81]. Duda and colleagues (2016) applied machine learning to distinguish ASD from attention deficit hyperactivity disorder (ADHD) using a 65-item *Social Responsiveness Scale*. Bone et al. [39] trained their models to discriminate ASD subjects from healthy controls using the same *Social Responsiveness Scale* and the *Autism*

Diagnostic Interview-Revised score. Other studies aggregated items from the ADOS and scores from the *Autism Quotient* to accurately classify an ASD group. As a result of the wide variation in ASD behavioral measures, many studies have searched for brain-based biological markers to identify a common etiology across individuals with ASD. These brain-based biological markers are less subjective than behavioral measures and may represent potential targets for treatments. Currently, markers that are measurable via magnetic resonance imaging (MRI) are highly desirable because they can represent potential targets for both assessment and intervention [93]. Independent structural MRI studies have found differences in whole brain volume and the developmental trajectories between individuals with ASD and those who do not have ASD [7, 45, 63]. Other structural brain abnormalities associated with ASD include cortical folding signatures, showing in brain regions of the TPJ, anterior insula, posterior cingulate, lateral and medial prefrontal, corpus callosum, intra-parietal sulcus, and occipital cortex [123, 163, 201, 246]. Evidence also shows that an accelerated expansion of the cortical surface area, but not cortical thickness, can lead to the early overgrowth of the ASD brain [110], while other studies suggest that individuals with ASD tend to have thinner cortices and reduced surface area as an effect of aging [85].

Machine learning (ML) has been introduced to the neuroimaging field to identify the abnormal brain regions in individuals with ASD, see Figure 1.5. Support vector machines (SVM) is an algorithm that generates high classification accuracy without requiring large sample sizes to avoid over-fitting [170]. The SVM algorithm is able to classify ASD from corresponding controls using extracted features from functional connections and grey matter volume [59, 62, 107, 140, 204]. Other algorithm-based classifications of ASD include the random forests (RF) algorithm, which uses random

ensembles of independently grown decision trees, and deep neural networks [61, 146]. Although these studies have proven accurate for classifying ASD, they have failed to identify precise neuroimaging-based biomarkers. The majority of studies have adopted data from the *Autism Brain Imaging Data Exchange (ABIDE)* dataset collected from 24 international brain imaging laboratories. The ABIDE dataset includes 1112 existing resting-state functional magnetic resonance (rs-fMRI) imaging datasets. It also includes the corresponding structural MRI and phenotypic information from 539 individuals with ASD and 573 age-matched NT controls [68, 127]. Classification across a heterogeneous population is extremely challenging. There is a huge amount of considerable variation in demographic and phenotypic profiles of participants. Such variation becomes more apparent and problematic especially when neuroimaging data are collected from multiple acquisition sites, such as ABIDE [68, 127]. Many factors can lead to such variances in datasets such as scanner hardware, imaging protocols, operator characteristics, demographics of the regions, acquisition site-specific problems, greatly affecting the classification performance. This problem is especially relevant for ASD given its notable heterogeneity. It is often difficult to collect neuroimaging data from individuals with autism given the loudness of the scanner and the challenges to remain still. In fact, most individual site datasets have small sample sizes, which can lead to overfitting and classification inaccuracies. Moreover, many traditional ML algorithms are designed to classify large amount of data (e.g., ABIDE) rather than optimize the selection of features, while the ultimate goal for machine learning based diagnostic classification in neuroimaging is to identify discriminative features to provide insight into abnormal structure and dysfunctional connectivity patterns in the affected population [164].

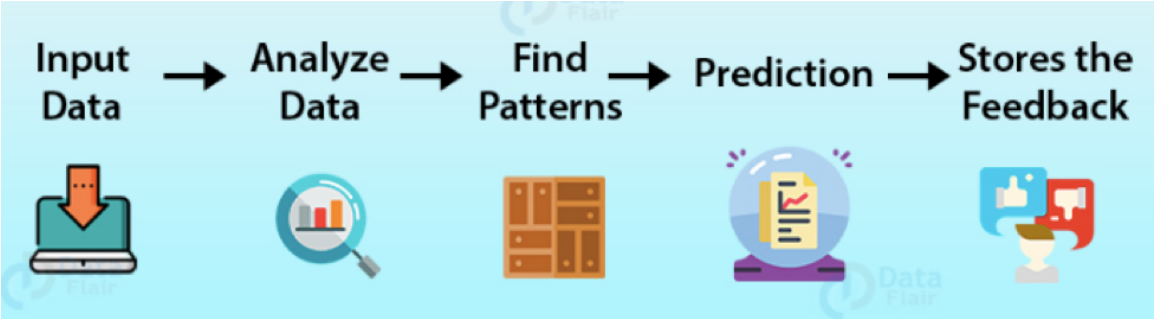

Figure 1.5: Simple Illustration of Machine Learning. [1]

1.5.1 Introduction of Chapter Three

Although some ML-based methods have been applied to ASD, the suitability of machine learning and the choice of algorithms with regard to the specific behavior examined, as well as the quality and quantity of the data obtained from individual studies, requires further investigation. Chapter 3 introduces a study that adopts a novel evolutionary algorithm, the conjunctive clause evolutionary algorithm (CCEA), to select features most significant for distinguishing individuals with and without ASD, and is able to accommodate datasets having a small number of samples with a large number of feature measurements. The dataset is unique and comprises both behavioral and neuroimaging measurements from a total of 28 children from 7 to 14 years old. Potential biomarker candidates including volume, area, cortical thickness and mean curvature in specific regions in the cingulate cortex, frontal cortex and temporal-parietal junction areas were identified. Behavioral features associated with theory of mind were selected. Additional classification models were developed to validate the selected features by CCEA using the k-nearest neighbors algorithm. Study findings demonstrate how machine learning tools can advance ASD research in the genre of big data to benefit this special population in the future.

Chapter 2

A Pilot Study Using Two Novel fMRI Tasks: Understanding Theory of Mind and Emotion Recognition Among Children With ASD

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2.1 Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder in which an individual's symptoms can vary from mild to severe. According to the most recent prevalence rates from the US Centers for Disease Control and Prevention (CDC), about 1 in every 54 individuals has ASD [58]. Although many theories exist about the pathology and causes of autism, such as genetic and environmental factors, ASD is a heterogeneous disorder without a specific known cause or cure. Language and intellectual impairments may or may not be characteristic of children with ASD, but the most significant challenges they face are difficulties communicating and interacting with others in social situations [92]. Early diagnosis and intervention (e.g., speech and language therapy, social cognitive behavioral intervention, etc.) targeting these social difficulties are especially critical if we wish to improve the social communication skills of children with autism, as well as help them build relationships, engage in activities with others, and be successful in school.

An important component of social communication and social interaction in children with ASD is theory of mind (ToM). ToM is the ability to reason about the thoughts and feelings of self and others, including the ability to predict what others will do or how they will feel in a given situation on the basis of their inferred beliefs [22, 23]. Difficulties with ToM are thought to lead to impairments in social interactions among individuals with ASD. It has been argued that individuals often encounter difficulties interacting with others appropriately within a social context when their abilities to interpret the beliefs, intentions, and emotions of others are impaired, [48, 126]. Individuals with ASD often have trouble interpreting or reading the

verbal and non-verbal communications of others, specifically in social interactions [9].

ToM abilities have been adopted as proxies to functioning level in ASD for several reasons: (1) the developmentally sequenced acquisition of ToM skills in childhood is well documented [215, 277]; (2) ToM tests have been used in a variety of populations and cultures [18, 28, 122]; and (3) ToM deficits ostensibly underlie social communication impairments in ASD [119, 254, 267]. Additionally, general ToM assessment is internationally applicable in that ToM skills develop in roughly the same manner across the world [247, 275, 276]. ToM abilities have also been proposed as a potential severity index in ASD: better ToM is associated with improved behavior towards social rules [263], better social interaction skills [41, 100], and increased language use [60, 116].

At a neural level, studies have established a ToM network involving the medial prefrontal cortex (mPFC), the posterior superior temporal sulcus (pSTS), the temporal parietal junction (TPJ), the precuneus, and the posterior cingulate cortex (PCC). More specifically, the mPFC is associated with mental state reflection; the pSTS is involved in inferring to other's actions; and the TPJ with understanding beliefs and socially relevant information [143, 205, 256]. Individuals with ASD exhibit decreased activation and connectivity among these identified ToM regions, as well as decreased connectivity in the frontal-medial, frontal-parietal and medial cerebellum anatomical networks [143, 205, 256]. The purpose of this study is to examine behavioral and neurobiological measures of emotions involving ToM, contributing to what is known about ToM markers at the brain and behavior levels that can distinguish those with and without ASD. In the review of the literature that follows, we discuss the development of emotion recognition as one aspect of ToM in neurotypical (NT)

and ASD populations surrounding happiness, sadness, surprise, embarrassment and desire-based emotion. This includes a description of how emotion recognition has been tested and measured at both a behavioral and neural level in individuals with ASD.

2.1.1 Emotion Recognition in Neurotypical Development

One particular aspect of ToM, emotion recognition, plays a critical role in an individual's ability to meaningfully engage in social communication and social interaction. Emotion recognition is the ability to discriminate between different facial expressions and is key to understanding empathy or the feelings of others. The present study focuses on three specific emotions (i.e., surprise, embarrassment, desire-based emotion) as they are critical aspects of ToM.

Happiness is considered to be the easiest recognized emotion while sadness is associated with the most negative affective reactions among the NT population [179]. Meta-analyses have found that the processing of emotional faces is associated with increased activation in a number of visual, limbic, TPJ and prefrontal areas, where happy and sad faces specifically also activate the amygdala [104]. Surprise conveys a sense of novelty or unexpectedness and most research indicates that accurate recognition of surprise will happen around the preschool years or even later among the NT population [132, 274]. One functional magnetic resonance imaging (fMRI) study suggests that rapid recognition of surprised faces is associated with greater brain activities in the right postcentral gyrus and left posterior insula [147]. Embarrassment is

often described as a "self-conscious" emotion that is associated with a feeling of shame or awkwardness around some action or statement [56,124,125,132]. Experiencing "embarrassment" does suggest some level of self-awareness that an "expected" behavior in a social context was unmet [31, 33, 86–88, 132, 169]. Embarrassment is evoked during negative evaluation following norm violations and supported by a fronto-temporo-posterior network. It often recruits greater anterior temporal regions, representing conceptual social knowledge [136]. Desire-based emotion recognizes the relationship between getting what you want and feeling happy and not getting what you want and feeling sad or disappointed. Thus, desire-based emotion can lead to positive emotions or negative emotions, depending on a fulfilled or unfulfilled desire [132,227,228]. There is abundant evidence that around the age of two, NT children understand desire-based emotion and can accurately predict emotional consequences when another's desire and the situational outcome are known (i.e., others are judged as "happy" if the outcome was wanted and "sad" if it was not) [291].

2.1.2 Emotion Recognition in ASD

Children with ASD have impairments in social interaction often due to a lack of understanding of emotions and the minds of others, as well as difficulty attending to social cues (e.g., gaze, facial expressions, body postures, etc.) [160]. Some studies have found that children with ASD use the lower part of the face to determine one's facial expression and often ignore or have difficulty identifying negative facial affects evident near the eyes (e.g., distress, fear) as early as the age of three [160]. However, other studies suggest that children with ASD have trouble recognizing emotions from the lower part of the face compared to NT children [160]. There is a wealth of

behavioral evidence showing that recognition of even more early developing emotions like happiness and sadness are impaired in individuals with ASD [10,66,194]. On the other hand, there is evidence of intact recognition of happiness in some individuals with ASD([11] as well as a "happy advantage" as recognition of happiness within ASD groups tends to be better than recognition of other emotions [70, 132, 162, 265, 271]. Better recognition of happiness is also associated with greater social competence [70,132]. The recognition of negative emotions including sadness is generally found to be impaired in ASD [67, 132, 160, 218, 271]. Poor accuracy during sadness recognition tasks is associated with higher symptom severity and poorer adaptive functioning in individuals with ASD [121].

Research has also demonstrated that during face recognition tasks, individuals with ASD show activity in brain areas typically related to the object perception pathway in NT individuals [156, 237], suggesting that individuals with ASD may be compensating for a lack of functionality in the core and extended face perception pathways by recruiting regions comprising more general object perception networks. This may explain why ASD individuals perform reasonably well on some behavioral tasks involving emotional face processing [199], perhaps by adopting a compensatory strategy.

The fusiform gyrus (FG), the superior temporal sulcus (STS), and the amygdala have been implicated in the aberrant neuropathology of ASD during face processing. In general, there is evidence for atypical patterns of brain activity in the form of hypoactivation of the FG, STS, amygdala and the occipital lobes, alongside hypoconnectivity of the FG in individuals with ASD. In addition, individuals with ASD demonstrate hypoactivation and hypoconnectivity in areas of the face perception

network, including the inferior frontal gyrus (IFG) [111], the inferior temporal gyrus (ITG) [111], and the middle frontal gyrus (MFG) [156]. These results demonstrate that atypical brain activation during emotional face perception is not restricted to the core face perception pathway, but also extends to other cortical areas related to executive functions such as attentional control and inhibition. Taken together, these findings suggest that atypical face perception in ASD is mediated by other factors in addition to pure visual perception.

The neural mechanisms underlying the interpretation of basic emotions such as happy and sad faces in ASD are well studied. Although most studies have reported decreased amygdala activation during emotional face processing (e.g., angry and fearful), one study has found greater right amygdala activation in the ASD group compared to the NT group when processing happy and sad faces [12, 69, 73, 109, 111, 210, 217]. Specifically, there was a greater positive functional connectivity between the right amygdala and ventromedial prefrontal cortex to happy faces but less positive functional connectivity between the right amygdala superior/medial temporal gyri [189]. Other studies also found that the ASD group showed greater bilateral activation in the amygdala, vPFC and striatum comparing to the NT group [72]. Due to high variability across fMRI studies, other brain regions have also been identified, but overall reduced brain activities when processing happy faces are observed in ASD groups [189, 250, 279]. The literature has also found consistent results that the ASD population is more sensitive to sad faces. When processing sad faces, ASD groups tend to show greater activation relative to control groups in the amygdala, vPFC, putamen, and striatum, and younger adolescents show greater activation than older adolescents [72, 279]. However, one study found decreased activities in mPFC among

the ASD group when processing sad faces [72].

Contrary to early-developing emotions (e.g., happy, sad, mad, scared) that are responses to situations, recognizing surprise among children with ASD appears to lag behind. Knowing that understanding one's own and others' desires, beliefs and values is a particular area of deficit for children with ASD, it is not unexpected they would be challenged in their ability to make sense of the concept of "surprise" [10, 66, 132, 178, 194, 231]. Desire-based emotion plays an important role when understanding and empathizing with others' thoughts and feelings [132, 216, 229, 278]. In general, the understanding of desire among children with ASD is very limited and they often are unable to generalize their understanding without explicit instruction and support in social contexts [132]. Surprise and desire-based emotions have only been examined at a behavioral level in individuals with ASD and little is known about their neural correlates. Children with ASD may show an emotional response of embarrassment, although to a lesser degree than their NT peers. Further, they seldom recognize embarrassment or express their experiences in situations of embarrassment. Often, they miss social gaffes where what is said is perceived as an inappropriate comment in a social context [33, 50, 132, 188, 239, 244, 259, 281]. Embarrassment has been studied at a neural level only among adults with ASD, with evidence suggesting altered circuitry in the mPFC, ACC, IFG, TPJ/pSTS, posterior cingulate cortex (PCC), and amygdala [124, 125, 136].

2.1.3 Purpose of the Study

Although ToM has been studied for decades, it still remains a challenging research area due to its multi-faceted composition. Although the neural mechanisms under-

lying ToM have been examined, few brain-based studies include children with ASD. Thus, a greater understanding of the brain-behavior connections associated with ToM in children will provide researchers a potential link between the biological mechanisms of ToM and behavioral characteristics. It will help lead to more efficient diagnostic processes and prognostic indicators for special populations like children with ASD. To facilitate increased understanding of this linkage, the current study will emphasize emotion recognition ToM with a specific focus on less well-studied and more complex emotions (i.e., surprise, embarrassment, and desire-based emotion). Surprise and embarrassment are particularly difficult for children with ASD to recognize [121, 265]. While desire-based emotions are easier for children with ASD to recognize, their understanding of these emotions is delicate and often requires explicit descriptions.

The current study is the first to examine the neural correlates of selected ToM constructs including desire-based emotions and more complex emotions (surprise, embarrassment) to establish connections between behavior and brain activities in children with ASD (i.e., 7 to 14 years old). We used The Theory of Mind Inventory-2 (ToMI-2) [131] and The Theory of Mind Task Battery (ToMTB) [134] to establish the behavioral patterns and identify differences between ASD and NT groups in their understanding of these less well-studied and complex emotions. We developed two novel fMRI tasks to identify brain regions associated with the recognition and processing of these emotions. Although our primary interest was in the neural response to recognition of more complex emotions requiring ToM (i.e., embarrassment and surprise), happy and sad faces were also included to provide a comparison with previous literature investigating recognition of basic emotions. We established brain activation patterns in both groups to further probe brain deficits and neural compensation

mechanisms being adopted by the ASD group. Specifically, we expected to see altered brain activity patterns among the ASD group in brain regions involved in the ToM neural network (e.g., mPFC, pSTS, cingulate cortex, and TPJ). Building upon findings from previous studies, the present study provides a deeper and more systematic understanding of the brain-behavior connections associated with ToM. This knowledge may lead to both behavioral and neural pathways for examining the impact of intervention research to achieve more normalized social performance. Such research might also help predict those brain-behavior profiles of children most likely to benefit from specific ToM or social cognitive based interventions, emphasizing the importance of interventions delivered at the cognitive level to bridge behavior with brain function [128].

2.2 Methods

2.2.1 Participants

Eleven children with ASD (1 female) and 22 NT children (7 females) participated in the study, in which 9 ASD and 19 NT subjects were included as they completed all of the the behavioral testing, magnetic resonance imaging (MRI) scans and fMRI tasks. The remaining subjects either completed only the behavioral testing, or withdrew from the study due to dental appliances precluding MRI scanning or because of study interruption due to COVID-19. The full study included 2-3 hours of baseline behavioral assessments along with a 1-hour brain scan including T1 imaging, T2 imaging, and two fMRI tasks. Since the understanding of surprise and embarrass-

ment has been shown to develop substantially between the ages of 5 and 8 years in NT populations [32–34], we set the minimum cut off age as 7 years old. We expanded the upper age limit to 14 years old to improve recruitment efforts given the challenges of recruiting subjects with ASD. All children were native English speakers.

We administered the Autism Diagnostic Observation Schedule-2 (ADOS-2) [175] and the Social Communication Questionnaire-Lifetime version (SCQ) [234] to confirm the clinical diagnosis for participants with ASD. Non-verbal intelligence and language levels were tested for all participants using the Universal Nonverbal Intelligence Test (UNIT-2) [44,184] and the Comprehensive Assessment of Spoken Language (CASL) [54], respectively, to ensure participants could demonstrate understanding of the instructions given in the behavioral and fMRI tasks. The UNIT-2 is a multidimensional assessment of intelligence for individuals with speech, language, or hearing impairments. It consists of nonverbal tasks that test symbolic memory, non-symbolic quantity, analogic reasoning, spatial memory, numerical series, and cube design. The CASL is an orally administered language assessment consisting of 15 subtests measuring language for individuals ranging from 3 to 21 years of age. For the present study, only those basic subsets that establish the CASL language core were used: Antonyms, Sentence Completion, Syntax Construction, Paragraph Comprehension, and Pragmatic Judgment.

Full demographic statistics are presented in Table 2.1. The groups differed on CASL and UNIT-2 scores, with the ASD children obtaining lower scores on both measures compared to the NT children. Because of these group differences in language and intellectual abilities, CASL and UNIT-2 scores were included as covariates in statistical analyses of ToM metrics.

Table 2.1: Demographics and T-tests Statistics including Mean, Range and p value

	NT Group (n=19)	ASD Group (n=9)	Group Difference
Age	10.2 (7-14)	11 (8-13)	$p = 0.36$
CASL	113 (89-132)	78.8 (40-121)	$p < 0.001$**
UNIT-2 Full Scale	111.9 (100-135)	96.2 (56-127)	$p < 0.05$*
ADOS-2	N/A	14 (9-21)	N/A
SCQ	N/A	22.3 (14-30)	N/A

2.2.2 Behavioral Measures of ToM

Two norm-referenced tools were used as behavioral outcome measures to assess ToM. The ToMI-2 [131] measures a parent's perception of their child's ToM understanding of 60 items using a 20-unit rating scale from "Definitely Not" to "Definitely". Primary caregivers use a vertical hash mark to indicate where on the continuous scale best represents their perceptions. Item, subscale, and composite scores range from 0-20. A higher number indicates a parent's greater confidence in their child's understanding of a particular ToM skill. The ToMI-2 items represent typical social interactions to ensure it is a socially and ecologically valid ToM index. The tool demonstrates excellent test-retest reliability, internal consistency, and criterion-related validity for neurotypical children and children with ASD as well as contrasting-groups validity and statistical evidence of construct validity (i.e., factor analysis) [131, 133, 166].

The ToMTB [134] is a direct measure of a child's understanding of ToM. It consists of nine ToM tasks presented as short vignettes in a story-book format arranged in ascending difficulty. For each of the nine tasks, children are provided with one correct response option and three possible distracters. There are 15 total questions asked, including memory control questions that must be answered correctly to get credit for

ToM understanding. The ToMTB has strong test-retest reliability [131, 134].

To examine subjects' ToM abilities, we used the total score of the ToMTB, total composite mean of the ToMI-2 (i.e., assessing overall ToM ability), early subscale mean of the ToMI-2 (i.e., assessing early developing ToMI ability such as regulating desire-based emotion and recognition of happy and sad), basic subscale mean of the ToMI-2 (i.e., assessing basic ToM ability such as recognition of surprise), and advanced subscale mean of the ToMI-2 (assessing advanced ToM ability such as recognition of embarrassment). We also included scores from single items assessing recognition of simple emotions such as happy and sad, as well as more complex emotions such as surprise and embarrassment.

2.2.3 MRI Acquisition

All neuroimaging data was acquired using the University of Vermont MRI Center for Biomedical Imaging 3T Philips Achieva dStream scanner and 32-channel head coil. The imaging protocol is based on that developed for the multicenter NIH-funded Adolescent Brain Cognitive Development (ABCD) study, which is derived from large studies such as the Human Connectome Project (HCP) and the Lifespan Connectome Project. The protocols make extensive use of simultaneous multislice imaging [47, 241, 242] (multiband SENSE) to accelerate functional and diffusion MRI acquisitions.

2.2.4 Task fMRI Parameters and Preprocessing

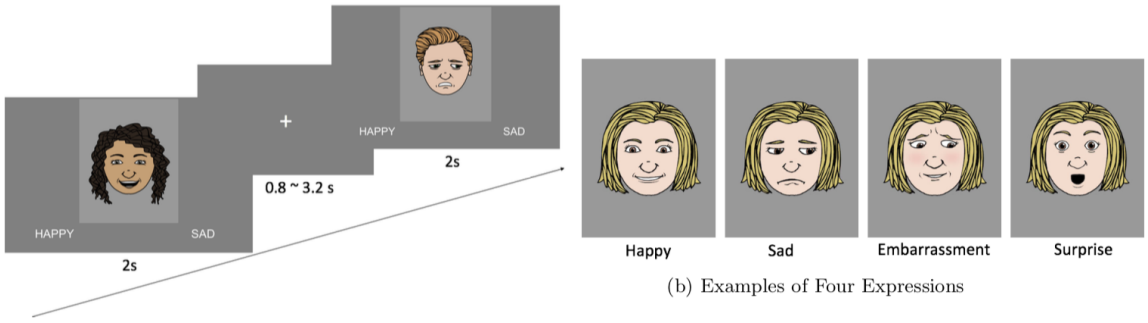
Task fMRI parameters were: TR 800ms, TE 30ms, flip angle 52 degrees, 2.4mm isotropic imaging resolution with a 216x216x144mm^3 field of view using a multiband acceleration factor of 6 (60 slices, no gap). For fMRI acquisitions, corresponding field maps were generated using pairs of reference acquisitions with opposite phase-encode directions. fMRI preprocessing used the pipelines developed as parts of the HCP [241]. The HCP functional pipeline corrects for EPI spatial distortions using magnetic field maps and realigns volumes to account for subject motion. Specifically, the fMRI surface pipeline was included in the preprocessing analysis while independent component analysis (ICA) denoising was not. Participants were trained to remain still during the scan in a mock scanner supplemented by video model (a short video demonstrating expected behavior in the scan) prior to each assessment. The HCP task fMRI pipelines were used for first- and second-level analysis of task fMRI data. These pipelines incorporate high-pass filtering and application of general linear models (GLMs) to model task parameters and nuisance regressors (e.g., motion parameters) [138, 139].

2.2.5 fMRI Emotion Recognition (fER) Task

This task was designed to assess emotion recognition, which was also a behavioral item tested on both ToMI-2 and ToMTB [131, 166]. The fMRI task required participants to either identify the emotions expressed in cartoon faces (emotion recognition) or judge the gender of the same emotional faces (perceptual control). Faces depicting happiness, sadness, surprise, and embarrassment were included. Since we did not

find existing stimulus/picture sets depicting embarrassment or of facial expressions of children in general, we hired a professional artist to create digital drawings of the cartoon face stimuli that matched the age of the participants and the style of pictures used in the ToMTB and ToMI-2. An independent sample of 163 NT participants from Amazon Mturk validated and selected the expressions that were recognized with 80% to 90% accuracy and were matched for valence. The final selection included eight different characters and two versions of each expression for each character, leading to 16 unique stimuli for each expression (see Figure 2.1 panel b for examples).

The fER task utilized a mixed design, with a block design for task (emotion recognition of surprise/embarrassment, emotion recognition of happy/sad, and perceptual control) and an event-related design for facial expression within each block (surprise/embarrassment or happy/sad). Across two runs, we presented 8 blocks of emotion recognition of surprise and embarrassment, 8 blocks of emotion recognition of happy and sad, and 8 blocks of perceptual control. Each block presented 8 faces in an event-related fashion for 2 seconds each with a jittered ISI (i.e., multiples of the TR, optimized using the optseq tool [102]. Participants pressed one of two buttons to indicate the emotional expression (surprise/embarrassment or happy/sad, in emotion recognition blocks) or the gender of the face (boy/girl, in perceptual control blocks); see Figure 2.1, panel a. An instructional cue (i.e., Label Emotion, Label Gender) was provided before each block. Between blocks there was an 8 second interval. The mixed design allowed us to not only create different contrasts between each emotion, but also between advanced emotion processing (i.e., recognition of combined embarrassment and surprise) with basic emotion processing (i.e., combined happy and sad).



(a) Timing of the fER Task

(b) Examples of Four Expressions

Figure 2.1: Illustration of the fMRI Emotion Recognition (fER) Task

2.2.6 fMRI Theory of Mind (fToM) Task

We developed this fMRI task to directly model the desire-based emotion task in the ToMTB [134]. Participants were required to infer the reaction of a cartoon character to a gift using the knowledge provided about the preferences of that character. Each trial was broken into three images: encoding, probe, and decision-making (see Figure 2.2). In the encoding image (2.4s), a child was seen holding a gift box. Two items were presented in thought bubbles displaying the preferences for that character. One item was presented with hearts to indicate the character likes the item, the other with an X over it to indicate the character dislikes that item. In the probe image (2s), a top view of the unwrapped gift box showed the desired/undesired item. Finally, in the decision-making image (2s), participants saw two images of the character's face expressing either happiness or sadness and respond by pressing a button to indicate which face best captured the reaction of the character to the gift. In control trials, participants saw an empty thought bubble and gift box and were asked at the decision-making step to indicate the gender of the cartoon face. There were 10 different characters and 30 unique items ranging from items commonly recognized as

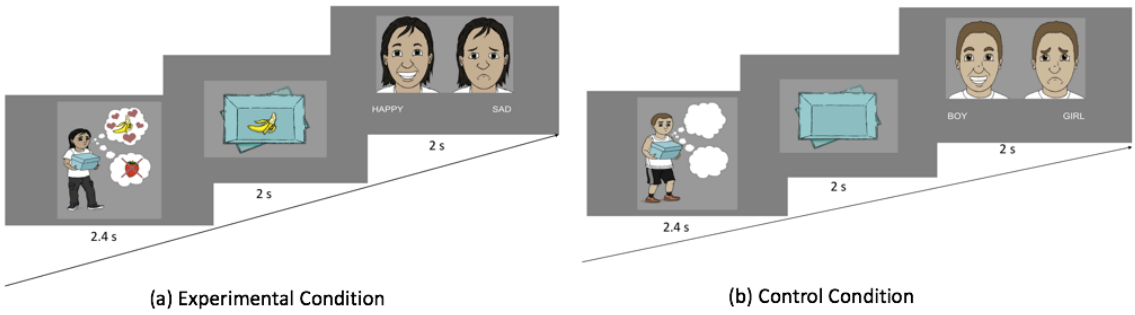


Figure 2.2: Illustration of the fMRI Theory of Mind (fToM) Task

desired by children (e.g., lollipop) to items commonly recognized as unwanted (e.g., spider). This task was presented in an event-related manner over 2 runs and included 15 trials where the character got what he/she likes, 15 trials where the character did not get what he/she likes, and 30 control trials, with a jittered inter-trial interval (ITI) of 0.8-3.2s.

2.3 Statistical Analyses

Behavioral analyses compared the ToM metrics from the ToMI-2 and the ToMTB, as well as the response time and accuracy from the two fMRI tasks. For analyses of the ToMI-2 and the ToMTB, group comparisons were performed using an analysis of covariance (ANCOVA) with group as a between-subjects factor and CASL score (i.e., language assessment) and UNIT-2 score (i.e., non-verbal intelligence assessment) as covariates. For the fER task, behavioral response times and response accuracy were evaluated for both NT and ASD groups using independent sample t-tests for: all conditions combined (overall), surprise condition, embarrassment condition, happy condition, sad condition, happy and sad conditions combined (HS, to examine basic

emotion processing), embarrassment and surprise condition combined (ES, to examine advanced emotion processing), and the control (gender) condition. For the fToM task, response times and response accuracy were evaluated for both NT and ASD groups using independent sample t-tests for: all conditions combined (overall), control (gender) condition, and experimental conditions (dislike and like conditions combined).

In order to detect neural activation related to the two fMRI tasks, first-level neuroimaging analyses were performed first. Vectors of stimuli onsets using the stimulus duration were created for each trial type and were convolved with a canonical double gamma hemodynamic response function to produce a regressor for each condition. Six motion regressors were included as covariates. For second-level neuroimaging group analyses, whole-brain between-group changes in activation patterns over time were assessed for each experimental condition using FSL's permutation-based non-parametric testing and threshold-free cluster enhancement to control for multiple comparisons [248]. Analyses were restricted to gray matter. Different group GLMs were constructed for each hypothesis separately. For the fER task, GLM models were constructed for contrasts between happy vs. gender, sad vs. gender, surprise vs. gender, embarrassment vs. gender, happy & sad vs. gender (HS, to assess basic emotion processing), and embarrassment & surprise vs. gender (ES, to assess advanced emotion processing). For fToM task, GLM models were constructed for contrasts between dislike & like (experimental) vs. control. CASL scores (i.e., language assessment) and UNIT-2 scores (i.e., non-verbal intelligence assessment) were also included as covariates in the permutation analysis of linear models (PALM) for group comparisons [283].

Table 2.2: ToM Behavioral Measurements and ANCOVA Results

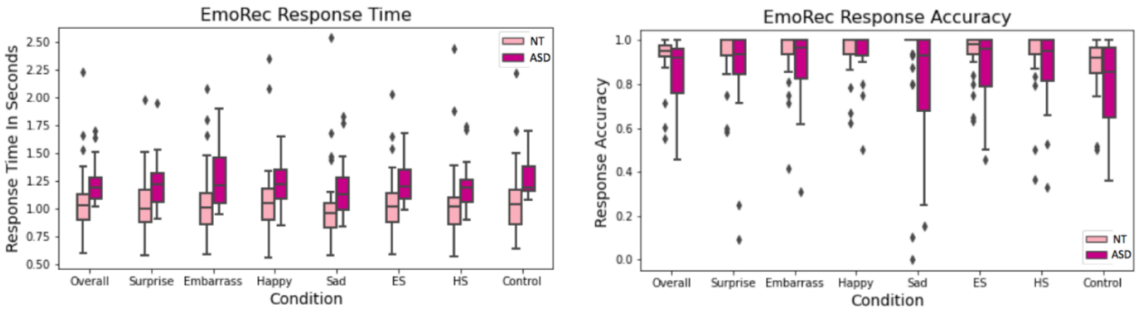
		NT Group (n=19)	ASD Group (n=9)	Group Difference
ToMTB		13.3(11-15)	11.1 (5-14)	$p = 0.38$
ToMI-2	*Total*	17.2 (11.5-19.3)	12.4 (9.1-17.6)	$p < 0.05$*
	Early Subscale	17.7 (13.8-20)	14.6 (11.6-17.9)	$p < 0.01$*
	Basic Subscale	18 (13.2-19.7)	14 (8.5-19.2)	$p = 0.12$
	Advanced Subscale	16 (8.3-18.9)	9.4 (6-16.4)	$p = 0.07$
	Happy	18.5 (14.1-20)	17.3 (12.5-20)	$p = 0.25$
	Sad	17.5 (7.1-20)	16.9 (13.1-20)	$p = 0.66$
	Surprise	17.8 (12.2-20)	15.3 (10.3-20)	$p = 0.07$
	Embarrassment	15.3 (5.8-20)	10.3 (4.8-20)	$p = 0.11$
	Desire-Based	18.9 (15-20)	16.7 (14.6-20)	$p = 0.09$

2.4 Results

2.4.1 Behavioral Results

When adjusted for covariates of the CASL (i.e., language assessment) and UNIT-2 scores (i.e., non-verbal intelligence assessment), the NT group had a significantly better performance on the ToMI-2 total score ($F(1,24)=4.48$, $p<0.05$) and the ToMI-2 early subscale score ($F(1,24)=7.76$, $p<0.01$). See Table 2.2.

On the fER task, the NT group responded significantly faster than the ASD group when considering all conditions together ($t(54)=2.56$, $p=0.01$), as well as in conditions of surprise ($t(54)=2.58$, $p=0.01$), embarrassment ($t(54)=2.64$, $p=0.01$), sadness ($t(54)=2.03$, $p<0.05$), control ($t(54)=2.73$, $p<0.01$), and ES (embarrassed + surprise) ($t(54)=2.77$, $p<0.01$); see Figure 2.3. There was no significant difference found for the happy condition ($t(54)=1.75$, $p=0.09$) or the HS (happy + sad) condition ($t(54)=1.95$, $p<0.06$). On this task the NT group also had a significantly higher response accuracy compared to the ASD group when considering all conditions together ($t(54)=2.55$, $p=0.01$), as well as in conditions of ES ($t(54)=2.29$, $p=0.03$) and control



(a) Response Time In Seconds

(b) Response Accuracy

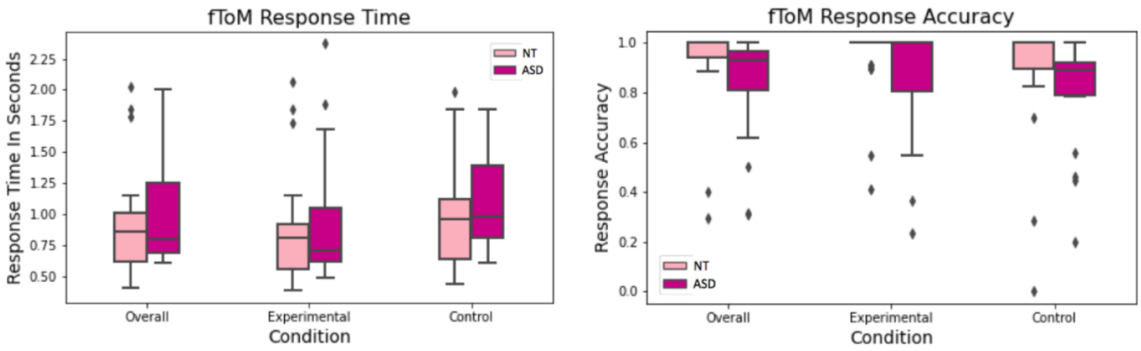
Figure 2.3: fMRI Emotion Recognition (fER) Task Response Time and Accuracy

($t(54)$=2.52, p=0.02). There was no significant difference in terms of response accuracy between the two groups in conditions of surprise ($t(54)$=1.92, p=0.06), embarrassment ($t(54)$=1.87, p=0.07), happiness ($t(54)$=0.77, p=0.44), sadness ($t(54)$=1.89, p=0.06), or HS ($t(54)$=1.77, p=0.08).

On the fToM task, there was no significant difference in response time between the NT and ASD groups for any of the comparisons: all conditions combined ($t(54)$=1.27, p=0.21), experimental condition ($t(54)$=1.14, p=0.26), and control condition ($t(54)$=1.33, p=0.19); see Figure 2.4. The NT group had a significantly higher response accuracy compared to the ASD group when considering all conditions combined ($t(54)$=2.21, p=0.03) and for the experimental condition only ($t(54)$=2.23, p=0.03). There was no significant difference in response accuracy for the control condition ($t(54)$=1.92, p=0.06).

2.4.2 Brain Activity Patterns

Cohen's D effect size maps were generated for each contrast of both fMRI tasks. The present study adopted a threshold of d=0.5 (medium) to show the effect size of



(a) Response Time In Seconds

(b) Response Accuracy

Figure 2.4: fMRI Theory of Mind (fToM) Task Response Time and Accuracy

the difference in brain activities between the ASD and NT groups. The contrast was conducted as ASD minus NT. Positive d-values (hot colors) indicate greater activation in the ASD group compared to the NT groups, while negative d-values (cool colors) indicate less activation in the ASD group compared to the NT groups.

In the fER task, when recognizing happy faces the ASD group showed greater brain activation in the mPFC and the angular gyrus (AG) compared to the NT group (see Figure 2.5), but less brain activation in most areas of the frontal cortex, the temporal lobe especially around the inferior temporal sulcus (ITS), and the TPJ. When recognizing sad faces, the ASD group showed greater brain activation in the left temporal lobe, the left AG, the anterior and posterior cingulate cortex, the occipital lobe, and the perirhinal area, but less brain activation in the right temporal lobe, the mPFC, and the inferior part of the post central gyrus. When combining happy and sad faces (i.e., HS), the brain activation pattern was similar to recognizing sad faces alone.

When recognizing surprised faces in the fER task, the ASD group showed greater brain activation in the left AG, the left temporal pole and STS, the left anterior and

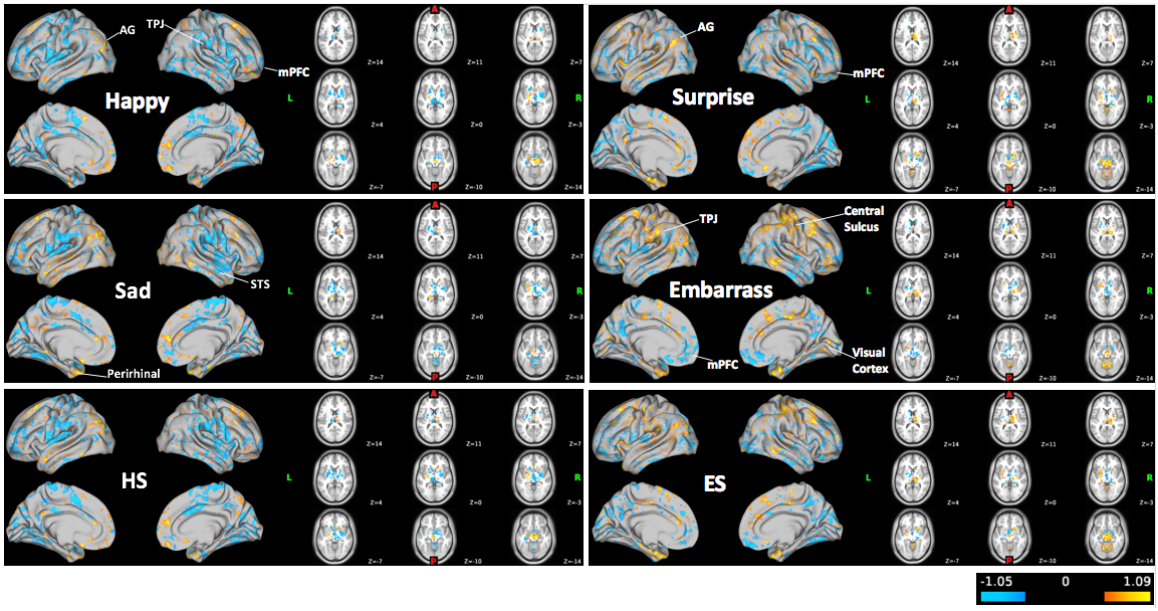


Figure 2.5: fMRI Emotion Recognition (fER) Task Brain Activation CohenD Maps, thresholded at d=0.5

posterior cingulate cortex, and the perirhinal area, but less brain activities in the visual cortex and the mPFC, comparing to the NT group (see Figure 2.5). When recognizing embarrassed faces, the ASD group showed greater brain activities in the TPJ, the AG and the right pre and post central gyrus, the visual cortex and the perirhinal area, but less brain activities in the mPFC. When combining surprise and embarrassed faces (i.e., ES), the brain activation pattern was similar to recognizing embarrassment faces alone.

In the fToM task examining desire-based emotions, the ASD group showed greater brain activation in most of the frontal regions especially around the right mPFC, the AG, the cingulate cortex, and the posterior STS, but less brain activation in the left TPJ and the left temporal lobe, comparing to the NT group (see Figure 2.6).

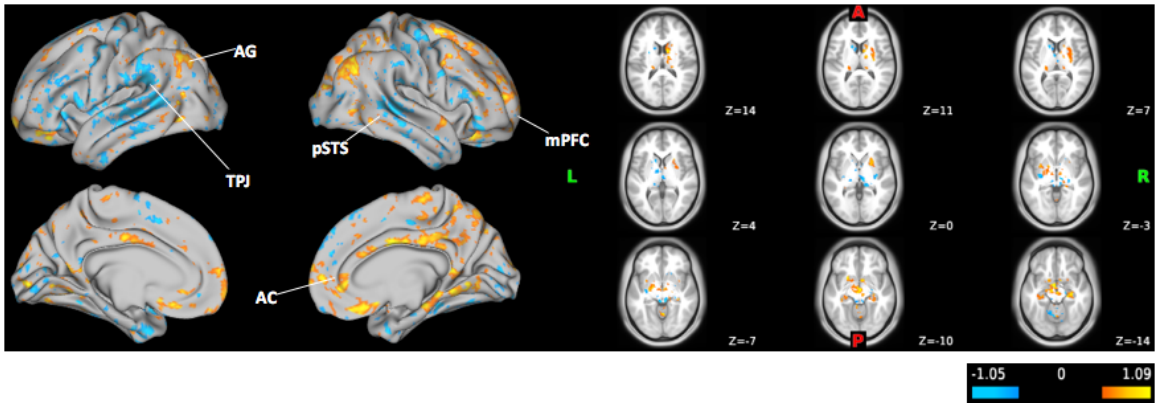


Figure 2.6: fMRI Theory of Mind (fToM) Task Brain Activation CohenD Maps, thresholded at d=0.5

2.5 Discussion

The current study adopts behavioral and neuroimaging measurements to examine the brain-behavior connections of ToM among children with ASD, specifically in the area of emotion recognition. The results demonstrate behavioral impairments and different brain activation patterns when performing ToM-related tasks in the ASD group compared to the NT group. Scores of behavioral tests suggest that the ASD group has poorer abilities and skills in multiple ToM metrics assessed by the ToMI-2 [131] and ToMTB [134] before taking language and non-verbal intelligence levels into account. Specifically, as predicted, the ASD group has more difficulty in recognizing and processing surprise, embarrassment and desire-based emotions, but are equally as good as NT participants at recognizing and processing happy and sad emotions. However, when language and non-verbal intelligence levels are considered, the group differences are only apparent in the ToMI-2 total and early subscale domains. These findings suggest that impairments of ToM abilities are largely associated with lan-

guage and intellectual levels, especially during more complex emotion recognition. In addition, these findings are consistent with the diagnostic criteria and other common challenges in ASD, including language and intellectual impairments and social challenges requiring advanced ToM abilities.

According to the results from the fER task, the ASD group takes longer to recognize facial expressions of surprise, embarrassment and sadness. This phenomenon is especially apparent when combining conditions of surprise and embarrassment (ES). This is consistent with previous studies suggesting intact ability for recognizing happiness in children with ASD [11] but impairments in recognizing sadness [11,67,218,271]. There are more severe impairments among children with ASD for recognizing surprise and embarrassment compared to happiness and sadness, as these advanced emotions require more cognitive processes [121, 265]. Thus, it makes sense that the ASD group needs more time to recognize embarrassment and surprise faces. In addition, the ASD group does not recognize surprise and embarrassment faces as accurately as the NT group. Results from the fToM task also indicate poorer performance (i.e., response accuracy) in processing desire-based emotion in the ASD group than the NT group, providing evidence that children with ASD have impaired skills in understanding ToM-associated desire-based emotion.

The brain activation pattern generated by the novel fMRI tasks demonstrate some consistent findings from previous literature. Specifically, when recognizing basic emotions such as happy and sad, the ASD group displays unusual brain activation patterns in the mPFC, the temporal sulcus, and the AG, compared to the NT group. In addition, compared to happiness, recognition of sadness in the ASD group seems to engage a more diverse range of brain regions including the occipital lobe, the left tem-

poral lobe and the perirhinal area associated with the amygdala. This implies that the ASD population has more difficulty recognizing sadness compared to happiness as there is greater brain effort as well as different brain areas that are recruited as compensatory mechanisms [11, 67, 70, 121, 162, 218, 232, 265, 271]. On the other hand, when recognizing happiness, there is less brain activation in the TPJ but more brain activation in the AG among the ASD group as compared to the NT group. Multiple studies have established the collaborative relationship between the TPJ and AG during ToM-related tasks among children with ASD, where the AG would display significantly increased activation if a particular ToM task required TPJ activation [135]. When recognizing more complex emotions such as surprise and embarrassment, the ASD group displayed more brain activation in the left AG but less brain activity in the mPFC area compared to the NT group. This suggests that advanced emotion recognition requires more ToM related abilities than abilities related to executive functions among the ASD group. It also seems that ToM requires more effort for the ASD group to recognize embarrassment compared to surprise as the ASD group engages in more brain activation in regions of the TPJ, the pre and post central gyrus, the visual cortex and the perirhinal area. This implies that the recognition of embarrassment requires more visual information processing and advanced ToM abilities, and may trigger the brain's fear center [27, 105, 193]. When processing desire-based emotion, the ASD group displays more brain activity around the right mPFC, the AG, the anterior cingulate cortex, and the posterior STS, but less brain activity around the left TPJ and the left temporal lobe, compared to the NT group. It is obvious that desire-based emotion processing is associated with traditional ToM related brain network including the TPJ, the STS, and the cingulate cortex. With decreased brain

activation in the TPJ area, the ASD group seems to engage the AG as a compensatory mechanism. In addition, the ASD group showed increased brain activity in the mPFC area compared to the NT group suggesting the possibility of recruiting more executive control regions to process the task to compensate for poorer ToM abilities.

As a pilot study, one major contribution of the present study is the successful implementation of two novel fMRI tasks targeting emotion recognition and processing associated with ToM. To our knowledge, this is the first time a set of facial stimuli were able to be adapted to an fMRI task to include expressions of surprise and embarrassment using the faces of children. It is also the first time that neural mechanisms underlying desire-based emotion processing are examined through fMRI. Further, these tasks are directly adapted from the ToMTB and ToMI-2 which allows comparison between behavioral and neuroimaging measurements. In addition, nearly all behavioral tests of ToM currently available only examine one or a few aspects of ToM; however, the ToMI-2 and ToMTB used in the present study are multi-faceted tools that cover several aspects of ToM (e.g., emotion recognition, false belief, perspective taking etc.), including information from both a parent and the child. These tools have helped to identify specific domains in ToM that are a struggle for ASD children. The present study has also identified brain activation maps associated with such domains by using two novel fMRI tasks. These maps provide evidence of how different brain regions are involved in the ability to reflect on mental states (i.e., mPFC), understand other's actions (i.e., pSTS), integrate relevant social information (i.e., TPJ), create and process emotions (i.e., cingulate cortex), and regulate negative emotions (i.e., amygdala) [72, 143, 205, 256, 258].

2.6 Limitations

Studies using MRI/fMRI technology face the typical challenges for any population with the requirements for tolerating loud noises, remaining still during the assessment and managing feelings of claustrophobia. For an ASD population these challenges are exacerbated, particularly in the recruitment phase of the study and in obtaining usable data. These challenges along with children being fitted with dental pieces precluded our ability to complete the MRI/fMRI images and COVID restrictions further limited access to an ASD population.

To address the challenges for using MRI/fMRI, all participants participated in a mock scanner experience. They viewed two videos explaining the process including one video specifically made to rehearse the experience. These strategies supported the successful participation of many of the participants with ASD but not all, which led to missing data.

As a part of our recruitment efforts, we expanded the age limit to 14 years old. The age of the participants in this study ranged from early childhood to the early adolescent period, typically an ideal age range to measure brain size while considering other possible neuroanatomical variables. Importantly, as the brain continues to grow and change into adulthood with rapid and significant development among adolescence [155,195], the interpretation of the results provides insights for children in general, but does not provide age-specific information. Further, language abilities varied, so the possibility exists that participants may not have fully comprehended the instructions of the fMRI tasks and hence given wrong or negligent responses. To address these concerns, all participants were provided with in-person introductions for both tasks

which were also practiced on a computer with the same response device outside the scanner to ensure correct understanding and performance. During the scan, a research team member monitored the response signal box in the monitor room at all times to reassure that participants were paying attention to the task and following task instructions.

2.7 Conclusions and Implications

Currently, the diagnosis of ASD is based on behavioral symptoms alone. Delays in diagnosis of ASD can be 13 months and longer for minority and lower socioeconomic status groups [35, 57, 180, 181, 190, 225, 280]. It is also believed that a substantial number of individuals on the spectrum remain undetected [260]. Children with ASD are a challenging population to engage in experimental procedures that have specific task requirements and involve neuroimaging measurements. However, it is crucial to gather both behavioral and neuroimaging data to increase our understanding of the nature of the social deficits characteristic in ASD. This is important if we wish to advance the diagnostic process and implement intervention methods for which we are able to show positive behavioral and neural outcomes. Insights derived from this study are expected to help scientists and physicians understand how social deficits surrounding ToM in ASD are associated with the brain. By taking advantage of such knowledge, we might be able to offer insights into the development of neuroanatomical diagnostic criteria to allow for more efficient diagnosis and early identification of high-risk populations. It might also help provide a vehicle for examining neural and behavioral outcomes following individualized treatment methods. Although the

present study has some limitations including a relatively small sample size, the successful implementation of two novel fMRI tasks among children with ASD and the comprehensive findings from both behavioral and neuroimaging perspectives should stimulate future research when working with special populations such as those with ASD.

2.8 Supplemental Materials

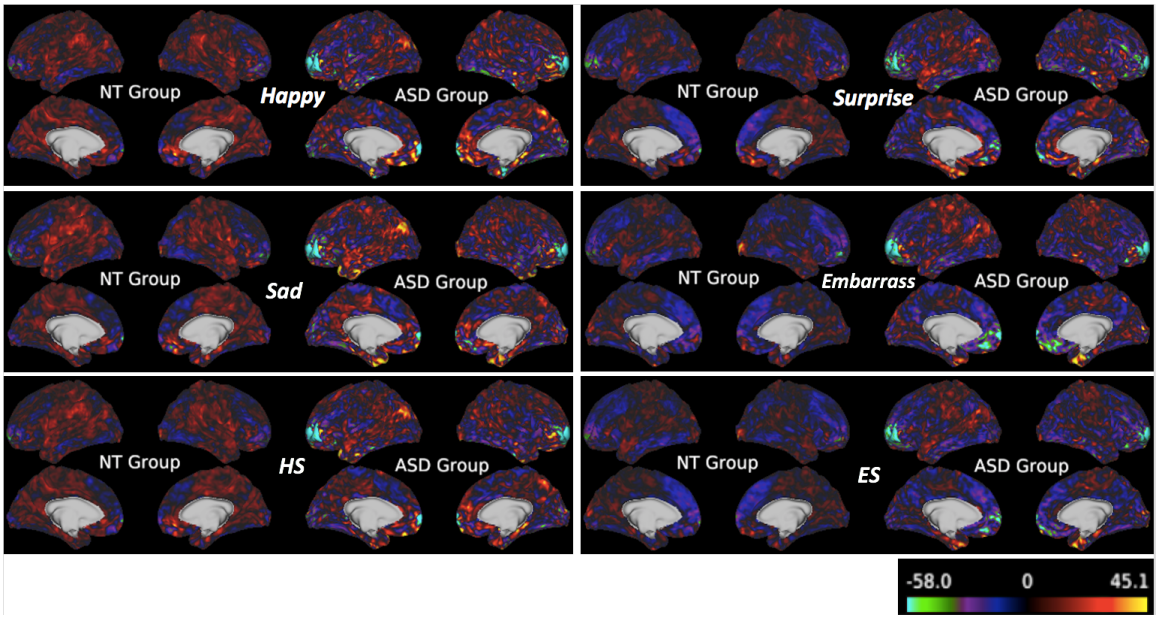


Figure 2.7: fMRI Emotion Recognition (fER) Task Brain Activation Beta Maps. Beta maps corresponding to voxel-wise mean beta values calculated from the GLM model for each group show the general activation patterns for each contrast. ASD group shows apparent decreased brain activities in the frontal pole region for all conditions and increased brain activities in the angular gyrus and the mPFC when recognizing happy and sad faces.

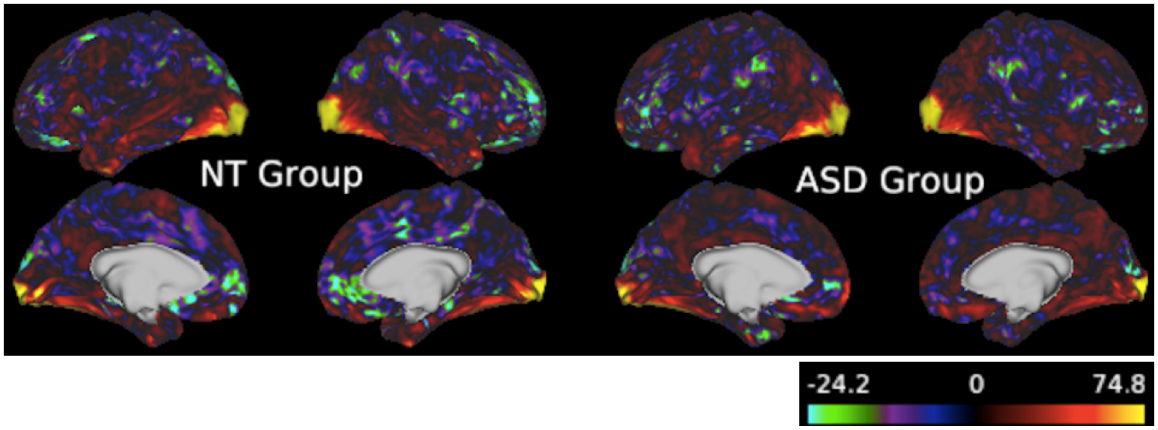


Figure 2.8: fMRI Theory of Mind (fToM) Task Brain Activation Beta Maps. Beta maps corresponding to voxel-wise mean beta values calculated from the GLM model for each group show the general activation patterns. Both groups show apparent increased brain activities in the visual cortex.

Chapter 3

Identifying Neuroanatomical and Behavioral Features for Autism Spectrum Disorder Diagnosis in Children using Machine Learning

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3.1 Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder in which an individual's symptoms can vary from mild to severe. It is characterized by significant social, communication, and behavioral challenges [171]. According to the most recent report from the Center for Disease Control and Prevention (CDC), the number of children in the U.S. diagnosed with ASD is about 1 in every 54 in year 2016 [58]. While genetic and environmental factors have been linked to the development of ASD, at present there is no identified cause or cure for ASD.

ASD is characterized by impairments in social interaction and the presence of restricted and repetitive behaviors, interests, or activities [9, 37, 97, 168]. Children with ASD may not show any symptoms until age two or later [38, 152]. Currently, the diagnosis of autism is based on behavioral symptoms alone: 1) impairments in social communication and interaction; and 2) the presence of restricted and repetitive behaviors, interests, or activities [9, 37, 97, 168]. There are two common behavioral assessment tools guiding the diagnostic process: The Autism Diagnostic Observation Schedule-Second edition (ADOS-2) and The Autism Diagnostic Interview-revised (ADI-R) [173,174]. However, a typical diagnostic appointment consists of evaluations lasting several hours at a designated clinical office. Due to the rigorous and time-consuming nature of ASD diagnostic examinations, the demand exceeds the capacity to see patients. As a result, many diagnostic centers have expanding wait lists for appointments. This bottleneck can translate to delays in diagnosis of 13 months and longer [35, 38, 57, 180, 181, 190, 225]. It is also believed that a substantial number of individuals on the spectrum remain undetected [260]. With growing awareness of

ASD, there is a high demand for a faster and automated ASD diagnostic approach that might allow for more efficient diagnosis and early identification of high-risk populations [208].

Building an automated diagnostic and predictive model of ASD is timely as many studies have adopted machine learning approaches to identify significant biomarkers that include both behavioral and biological features. Duda and colleagues (2016) applied machine learning to distinguish ASD from attention deficit hyperactivity disorder (ADHD) using the Social Responsiveness Scale for children between 5 to 13 years old [81]. Bone et al. (2015) trained their models to diagnose autism against healthy controls using the same Social Responsiveness Scale and the Autism Diagnostic Interview-Revised score for children between 5 to 17 years old [39]. Other studies aggregated items from the ADOS and scores from the Autism Quotient (AQ) to accurately classify an ASD group [13]. However, one limitation of using these behavioral outcome measures to classify participants is that they can be interpreted as being subjective. Furthermore, these studies identify a wide range of features depending on which models and tests are used. Consequently, the ability to identify more consistent ASD markers using neuroimaging measures to supplement behavioral measures becomes important.

As a result of the wide range and subjective nature of behavioral measures used in diagnosing ASD, many studies are exploring brain-based biological markers (e.g., measurable via magnetic resonance imaging (MRI)) to identify a common etiology across individuals with ASD. Currently, these less subjective markers are attractive not only for diagnostic purposes, but as possible targets for interventions [93]. Independent structural MRI studies have found differences in whole brain volume

and the developmental trajectories between individuals with ASD and those without ASD [7,45,78,123,163,201,246,266,270]. Other structural brain abnormalities associated with ASD include cortical folding signatures that appear in the following regions of the brain: temporal-parietal junction, anterior insula, posterior cingulate, lateral and medial prefrontal cortices, corpus callosum, intra-parietal sulcus, and occipital cortex [7, 45, 78, 123, 163, 201, 246, 270]. Evidence also shows that an accelerated expansion of cortical surface area, but not cortical thickness, causes an early overgrowth of the brain in children with ASD [110], while other studies suggest that individuals with ASD tend to have thinner cortices and reduced surface area as an effect of aging [85]. With these clear brain differences among those with and without ASD, it therefore is informative and critical to look for brain-based ASD biomarkers.

Machine learning (ML) has been introduced to the neuroimaging field to identify the abnormal brain regions in individuals with ASD. The support vector machine (SVM) is an algorithm that avoids overfitting and is known for high classification accuracy without requiring large sample sizes. It has been used to classify ASD from corresponding control participants using extracted features from functional connectivity metrics and grey matter volume [59, 62, 107, 140]. Other ASD applications of ML classifiers include deep neural networks [204] and the random forest (RF) algorithm; the latter uses random ensembles of independently grown decision trees [61]. Although these methods have demonstrated high accuracy for classifying ASD, to our knowledge, they have not been used to identify input variables most closely associated with ASD (i.e., feature selection). In addition, the majority of studies use data from the Autism Brain Imaging Data Exchange (ABIDE) dataset, which includes 1112 existing resting-state functional MRI (rs-fMRI) datasets with corresponding structural

MRI and phenotypic information from 539 individuals with ASD and 573 age-matched typical controls between the ages of 7 and 64 collected from 24 international brain imaging laboratories [68].

Classification across a heterogeneous population is challenging [127, 148], particularly when neuroimaging data are pooled from multiple acquisition sites, such as the ABIDE dataset, which has considerable variation in demographic and phenotypic profiles. Data variance introduced via scanner hardware, imaging protocols, operator characteristics, regional demographics, and other site-specific acquisition factors can affect the classification performance. This problem is especially relevant for ASD given the inherent heterogeneity of the population. It is often difficult to collect neuroimaging data from individuals with ASD given the loudness of the scanner and difficulties participants have remaining still. In fact, most individual site datasets have small sample sizes that can lead to overfitting and classification inaccuracies using traditional ML algorithms. Moreover, while the ultimate goal for ML-based diagnostic classification in neuroimaging is to identify discriminative features that provide insight into abnormal structure and dysfunctional connectivity patterns in the affected population [164], many of the ML algorithms applied to ASD were designed to classify large amounts of data (e.g., ABIDE) rather than optimize the selection of input features.

The drivers or markers of ASD are likely the result of a complex interaction of factors with no single factor (i.e., main effect or univariate model) driving the system. As such, traditional statistical tools (e.g., logistic regression) that search for univariate drivers of ASD are unlikely to find consistent patterns. Thus, ML techniques that explore large search spaces for multivariate interactions are both needed and becoming

popular in helping to elucidate the complex interactions in systems such as ASD. Our study employs one such ML tool: an evolutionary algorithm [186] called the conjunctive clause evolutionary algorithm (CCEA) [115]. The CCEA was specifically designed to efficiently explore large search spaces for complex interactions between features and some associated nominal outcome (e.g., ASD or neurotypical (NT)). In addition, the CCEA has built-in tools to prevent overfitting to produce easily interpretable parsimonious models.

This study examines the validity of using the CCEA for feature selection in ASD, particularly to address traditional statistical challenges associated with datasets having small sample sizes and a large number of feature measurements. Additionally, the selected features are validated and used for diagnostic classification by applying a separate and more traditional ML classifier (i.e., the k-nearest neighbors (KNN) algorithm). The dataset in this present study has a relatively large number of features, consisting of both behavioral and neuroimaging measurements. The behavioral measurements include scores of language ability, intellectual ability, and theory of mind (ToM). The neuroimaging measurements include brain volume, brain surface area, cortical thickness, and cortical curvature extracted from MRI whole-brain T1-weighted scans. These features were collected from a total of 28 children ages 7 to 14, of which 9 children had been diagnosed with ASD. Only a subset of these 28 children were used for feature selection in the CCEA (7 children with ASD and 14 NT children), as another subset (2 children with ASD and 5 NT children) were enrolled at a later time (i.e., after the CCEA was trained). While this later cohort was not included in the CCEA feature selection analysis, it was included in the subsequent validation and predictive KNN modeling.

Using the CCEA, we aim to identify discriminative biomarkers and behavioral features to help develop an automatic diagnostic and predictive system for ASD. We believe this is the first study to:

- Select discriminative biomarkers among children from 7 to 14 years old and classify ASD.
- Include both behavioral and neuroimaging measurements in the feature selection model.
- Identify models (sets of features) that most strongly correlate to children with ASD given a dataset with a relatively small sample size (i.e., N=28) and large number of features (i.e., 247 neuroimaging features and 13 behavioral features).
- Develop a predictive ML model using input features selected by the CCEA.

3.2 Materials and Methods

3.2.1 Participants

A total of 9 children with ASD (1 female) and 19 NT children (7 female), ages 7-14, were enrolled in the study. In addition to the behavioral assessments described below, the ASD group also completed the ADOS-2 and the Social Communication Questionnaire-Lifetime version (SCQ) [234] to confirm their ASD diagnosis. Although diagnosis of ASD is typically done at an early age, the characteristics of ASD are long-term, and classification with additional neurobiological information at any age

recognizes the potential for brain-behavior comparisons with neurotypical populations. Potential changes behaviorally and neurobiologically at any age may also inform types, duration, and intensity of intervention that may influence these changes. Therefore although we test older children, this study is still informative for increasing the understanding of likely biomarkers of ASD.

3.2.2 Behavioral Measurements

All children participated in 2-3 hours of baseline behavioral assessments that included the Comprehensive Assessment of Spoken Language (CASL) [54], the Universal Nonverbal Intelligence Test-2 (UNIT-2) [44,184], the Theory of Mind Task Battery (ToMTB) [134] and the Theory of Mind Inventory-2 (ToMI-2) [131,133]. Measures of language and cognition are typical in the assessment of ASD, as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) requires an assessment of language and intellectual functioning beyond the diagnosis of ASD.

The CASL is an orally administered research-based assessment consisting of 15 subtests measuring language for individuals ranging from 3 to 21 years of age. For the present study, only those basic subsets that establish the CASL language core are used: Antonyms, Sentence Completion, Syntax Construction, Paragraph Comprehension, and Pragmatic Judgment. The UNIT-2 is a multidimensional assessment of intelligence for individuals with speech, language, or hearing impairments. It consists of nonverbal tasks that test symbolic memory, non-symbolic quantity, analogic reasoning, spatial memory, numerical series, and cube design.

ToM is a core deficit in ASD that is often used to explain the social impairment characteristic of the disorder. ToM is the ability to reason about the thoughts and

feelings of self and others, including the ability to predict what others will do or how they will feel in a given situation on the basis of their inferred beliefs [21, 23]. Scores from both ToMTB and ToMI-2 were included to provide representative measures of a child's social cognition level. The ToMTB and ToMI-2 are two norm-referenced tools and behavioral tasks used as outcome measures to assess ToM [21, 23]. Scores from both ToMTB and ToMI-2 provide valid representations of a child's social cognition level. The ToMI-2 measures a parent's perception of their child's ToM understanding of 60 items using a 20-unit rating scale from "Definitely Not" to "Definitely". Primary caregivers use a vertical hash mark to indicate where on the continuous scale best represents their perceptions. Item, subscale, and composite scores range from 0-20. A higher number indicates a parent's greater confidence in their child's understanding of a particular ToM skill. The ToMI-2 items represent typical social interactions to ensure it is a socially and ecologically valid ToM index. The tool demonstrates excellent test-retest reliability, internal consistency, and criterion-related validity for neurotypical children and children with ASD as well as contrasting-groups validity and statistical evidence of construct validity (i.e., factor analysis) [131, 133, 166]. The ToMTB is a direct measure of a child's understanding of ToM. It consists of nine ToM tasks presented as short vignettes in a story-book format arranged in ascending difficulty. For each of the nine tasks, children are provided with one correct response option and three possible distracters. There are 15 total questions asked, including memory control questions that must be answered correctly to get credit for ToM understanding. The ToMTB has strong test-retest reliability [131, 134]. .

In selecting potential features for the CCEA, we included 13 behavioral features in total. These included the total score of the CASL, full scale score of the UNIT-2,

abbreviated score of the UNIT-2, total score of the ToMTB, total composite mean of the ToMI-2 (i.e., assessing overall ToM ability), early subscale mean of the ToMI-2 (i.e., assessing early-developing ToM abilities such as regulating desire-based emotion and recognition of happiness and sadness), basic subscale mean of the ToMI-2 (i.e., assessing basic ToM ability such as recognition of surprise), advanced subscale mean of the ToMI-2 (i.e., assessing advanced ToM ability such as recognition of embarrassment). Taken from another larger study about emotion recognition and ToM, we also included scores from single ToMI-2 items assessing recognition of simple emotions such as happiness and sadness, as well as more complex emotions such as surprise and embarrassment, which ASD children often find difficult to recognize and process [112, 124, 231]. Table 3.1 provides an overview of scores on the 13 behavioral measures. Results from independent sample t-tests found that NT participants scored significantly higher ($p<0.05$) than ASD participants on the CASL, UNIT-2 full scale, ToMTB, ToMI-2 total, ToMI-2 early subscale, ToMI-2 basic subscale, ToMI-2 advanced subscale, as well as ToMI-2 single items of surprise, embarrassment and desire-based emotion.

Table 3.1: Participant Behavioral Assessments Scores: NT vs. ASD

		NT Group (n=19)	ASD Group (n=9)	Group Difference
Age		10.2 (7-14)	11 (8-13)	$p = 0.36$
CASL		113 (89-132)	78.8 (40-121)	$p < 0.001$**
UNIT-2 Full Scale		111.9 (100-135)	96.2 (56-127)	$p < 0.05$*
Unit-2 Abbreviation		110.9 (91-124)	102 (67-121)	$p=0.16$
ToMTB		13.3 (11-15)	11.1 (5-14)	$p < 0.05$*
ToMI-2	*Total*	17.2 (11.5-19.3)	12.4 (9.1-17.6)	$p < 0.001$**
	Early Subscale	17.7 (13.8-20)	14.6 (11.6-17.9)	$p < 0.05$*
	Basic Subscale	18 (13.2-19.7)	14 (8.5-19.2)	$p < 0.001$**
	Advanced Subscale	16 (8.3-18.9)	9.4 (6-16.4)	$p < 0.001$**
	Happy	18.5 (14.1-20)	17.3 (12.5-20)	$p = 0.24$
	Sad	17.5 (7.1-20)	16.9 (13.1-20)	$p = 0.62$
	Surprise	17.8 (12.2-20)	15.3 (10.3-20)	$p < 0.05$*
	Embarrassment	15.3 (5.8-20)	10.3 (4.8-20)	$p < 0.05$*
	Desire-Based	18.9 (15-20)	16.7 (14.6-20)	$p < 0.05$*

3.2.3 MRI Acquisition and Preprocessing

All data were acquired using the MRI Center for Biomedical Imaging 3T Philips Achieva dStream scanner and 32-channel head coil at the University of Vermont (UVM). Parameters for T1 acquisition are TR 6.4s, TE 2.9s, flip angle 8 degree, 1mm isotropic imaging resolution with a 256x240mm^2 field of view and 225 slices. Participants watched three videos at home before coming to the MRI center. The first was a cartoon video explaining what an MRI is, and what one might experience while lying in an MRI scanner [261]. The second video, recorded at the UVM MRI mock scanner room, helped visualize the real setting and procedures a child would experience. The third video explained the procedures of wearing earplugs. All participants practiced laying still and became familiar with the scanner noise in the mock scanner room. The T1 structural scan was preprocessed using the Human Connectome Project (HCP) minimal preprocessing pipelines, including spatial artifact/distortion removal, surface generation, cross-modal registration, and alignment to standard space. These pipelines are specially designed to capitalize on the high-quality data offered by the HCP. The final standard space makes use of a recently introduced CIFTI file format and the associated grayordinates spatial coordinate system. This allows for combined cortical surface and subcortical volume analyses while reducing the storage and processing requirements for high spatial and temporal resolution data [106]. Brain anatomical features were extracted using FreeSurfer aparcstats2tabl script [102], including volume, cortical thickness, mean curvature, and area of all ROIs for each subject. These ROIs were defined using the automatic segmentation procedures that assign one of 37 labels to each brain voxel, including left and right caudate, putamen,

pallidum, thalamus, lateral ventricles, hippocampus, and amygdala [96]. There were 276 brain features included in total.

3.2.4 Conjunctive Clause Evolutionary Algorithm

We used an evolutionary algorithm to identify the features associated with ASD. The CCEA is a machine learning tool that searches for both the combinations of features associated with a given category (e.g., ASD) as well as their corresponding range of feature values [115]. The CCEA can find feature interactions even in the absence of main-effects, and can, therefore, identify feature combinations that would be difficult to discover using traditional statistics. The CCEA selects for the best conjunctive clauses (CCs) of the form:

$$CC_k = F_i \in a_i \wedge F_j \in a_j ..., \tag{3.1}$$

where F_i represents a risk factor i whose value lies in the range a_i; and the symbol $\wedge$ represents a conjunction (i.e., logical AND). One benefit of the CCEA is that it produces parsimonious models that are correlated with a select category (e.g., ASD). The models generated by the evolutionary algorithm can be described by their order or total number of features in the conjunctive clause. One example of a parsimonious second order conjunctive clause is: a person with a right hemisphere isthmus cingulate volume of 3,300 - 4,100 mm^3 AND a right hemisphere posterior cingluate volume of 4,100 - 6,200 mm^3 is more likely to have ASD than someone who does not meet these criteria.

The fitness of each conjunctive clause (CC) is evaluated using the hypergeometric probability mass function (PMF), and only the most-fit conjunctive clauses are saved. The hypergeometric PMF is not a p-value and thus, is not constrained by issues associated with what threshold is "significant" [203, 272, 273]. To prevent overfitting, the CCEA performs feature sensitivity on each conjunctive clause to ensure each feature contributes to the overall fitness. The sensitivity of each feature is calculated by taking the difference between the conjunctive clause fitness and the fitness when that feature is removed. Thus, a feature's sensitivity may be viewed as the amount of fitness that it contributes to the conjunctive clause. To visualize the fitness landscape, both positive predictive value and coverage are calculated. Positive predictive value (PPV) is the number of true positives divided by the sum of true and false positives; and class coverage is the number of true positives divided by the sum of true positives and false negatives (i.e., the percent of ASD individuals that match the conjunctive clause). In this work, the CCEA was run five times using the training set to ensure a more thorough search of the fitness landscape.

3.2.5 K-nearest Neighbors Algorithm and Leave-One-Out Cross Validation

In order to further validate the CCEA's selection of features capable of discriminating between children with and without ASD, we built a separate KNN classification model and used leave-one-out cross validation on all 28 subjects. The KNN is a classification algorithm that assumes that things that exist in close proximity (i.e., nearer to each other) are more similar. In this study, each subject was classified into one of two

output classes (i.e., ASD or NT) based on a plurality vote of its neighbors, with the subject being assigned to the class most similar to its k-nearest neighbors. When k = 1, then the subject is assigned to the class of a single nearest neighbor [191]. According to Efron (1982), "leave-one-out cross validation is a special case of cross validation where the number of folds equals the number of subjects in the data set. Thus, the KNN algorithm is applied once for each subject, using all other instances as the training set and using the selected subject as a single-item test set" [192, 235]. After model validation, we trained three separate KNN classifiers using a balanced dataset (6 NT and 6 ASD subjects) and feature sets identified by the CCEA to classify the remaining 16 subjects. See Table 3.2.

Table 3.2: Subject Inclusion and Distribution

Models		Subjects	Include Subjects Used In CCEA? N=21 (14 NT & 7 ASD)	Include Subjects from the Later Cohort That Was Not Used In CCEA? N=7 (5 NT & 2 ASD)
CCEA		NT = 14 ASD = 7	All	None
KNN Validation Model		NT = 19 ASD = 9	All	All
KNN Prediction Model	Training	NT = 6 ASD = 6	NT = 6 ASD = 4	NT= None ASD = 2
	Testing	NT = 13 ASD = 3	NT = 8 ASD = 3	NT = 5 ASD = None

3.3 Results

3.3.1 CCEA Feature Selection: 14 NT and 7 ASD

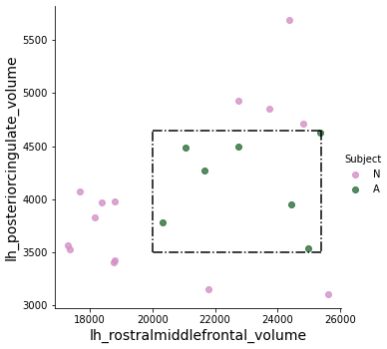
When using the CCEA for feature selection, 2438 CCs (i.e., models or sets of features) were generated ranging from first-order to fifth-order. The PPV of the 2438 models ranged from 46.47% to 100% and their class coverage ranged from 42.86% to 100%. Among these models, we looked for the most parsimonious (i.e., lowest order models) to draw meaningful conclusions and to avoid the overfitting that often occurs with higher-order models. As a result, we selected 8 second-order models (i.e., those having only two features) with the highest fitness (PMF) among the total 520 second-order models. These 8 "best performing" models each have 100% PPV and 100% class coverage, see Table 3.3. All of the features identified were brain anatomical features.

Table 3.3: Second-order CC model features and range of values

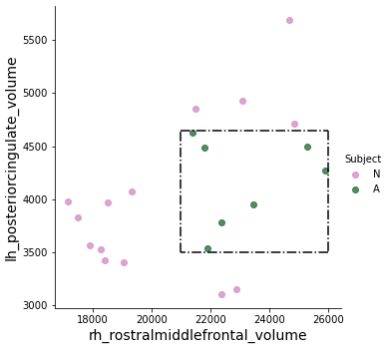
CC#	Feature One	Value	Feature Two	Value
113	lh posteriorcingulate volume	[3500, 4600]	lh rostralmiddlefrontal volume	[20000, 25000]
679	lh posteriorcingulate volume	[3500, 4600]	rh rostralmiddlefrontal volume	[21000, 26000]
1449	lh posteriorcingulate volume	[3500, 4600]	lh medialorbitofrontal thickness	[2.6, 2.8]
2199	lh posteriorcingulate volume	[3500, 4600]	rh rostralmiddlefrontal area	[6400, 8500]
887	rh isthmuscingulate volume	[3300, 4100]	rh posteriorcingulate volume	[4100, 6200]
1488	rh isthmuscingulate volume	[3300, 4100]	lh medialorbitofrontal thickness	[2.6, 2.8]
2200	rh isthmuscingulate volume	[3300, 4100]	rh rostralmiddlefrontal area	[6400, 8500]
2269	rh isthmuscingulate volume	[3300, 4100]	rh posteriorcingulate area	[1400, 2900]

Using CC 113 (Table 3.3) as an example, this second-order model can be inter-

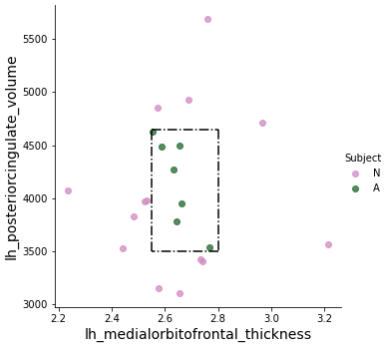
preted as: any subject whose posterior cingulate gyrus volume was within the range of 3500 to 4600 mm^3 AND left rostral middle frontal gyrus volume was within the range of 20,000 to 25,000 mm^3 would be classified as having ASD. The volume of the left hemisphere posterior cingulate gyrus and the volume of the right hemisphere isthmus of the cingulate gyrus were the two features to appear most frequently (i.e., four times) across all second-order models, suggesting that the volume of cingulate gyrus is a potentially important biomarker for ASD. Figure 3.1 provides a 2D visualization for the range of feature values (numerical boundaries) associated with these models and the placement of each subject within this range.



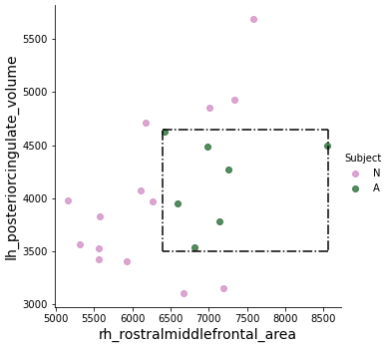
(a) CC113



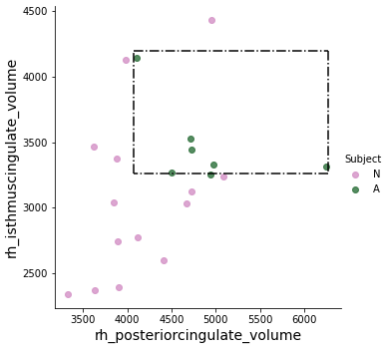
(b) CC679



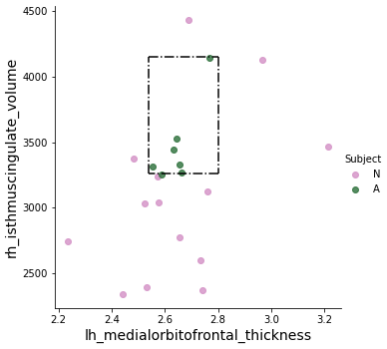
(c) CC1449



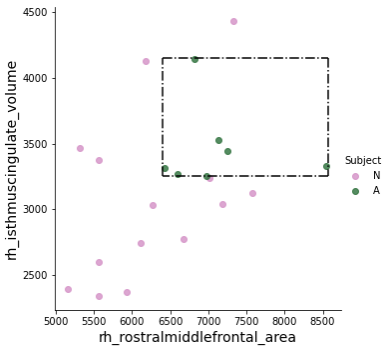
(d) CC2199



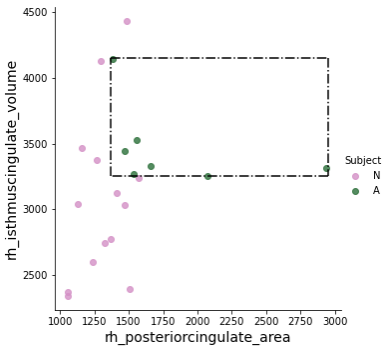
(e) CC887



(f) CC1488



(g) CC2200



(h) CC2269

Figure 3.1: 2D visualization of second-order CC models.

Green dots represent ASD subjects and group together within the rectangle defining the range of values in Table 3.3

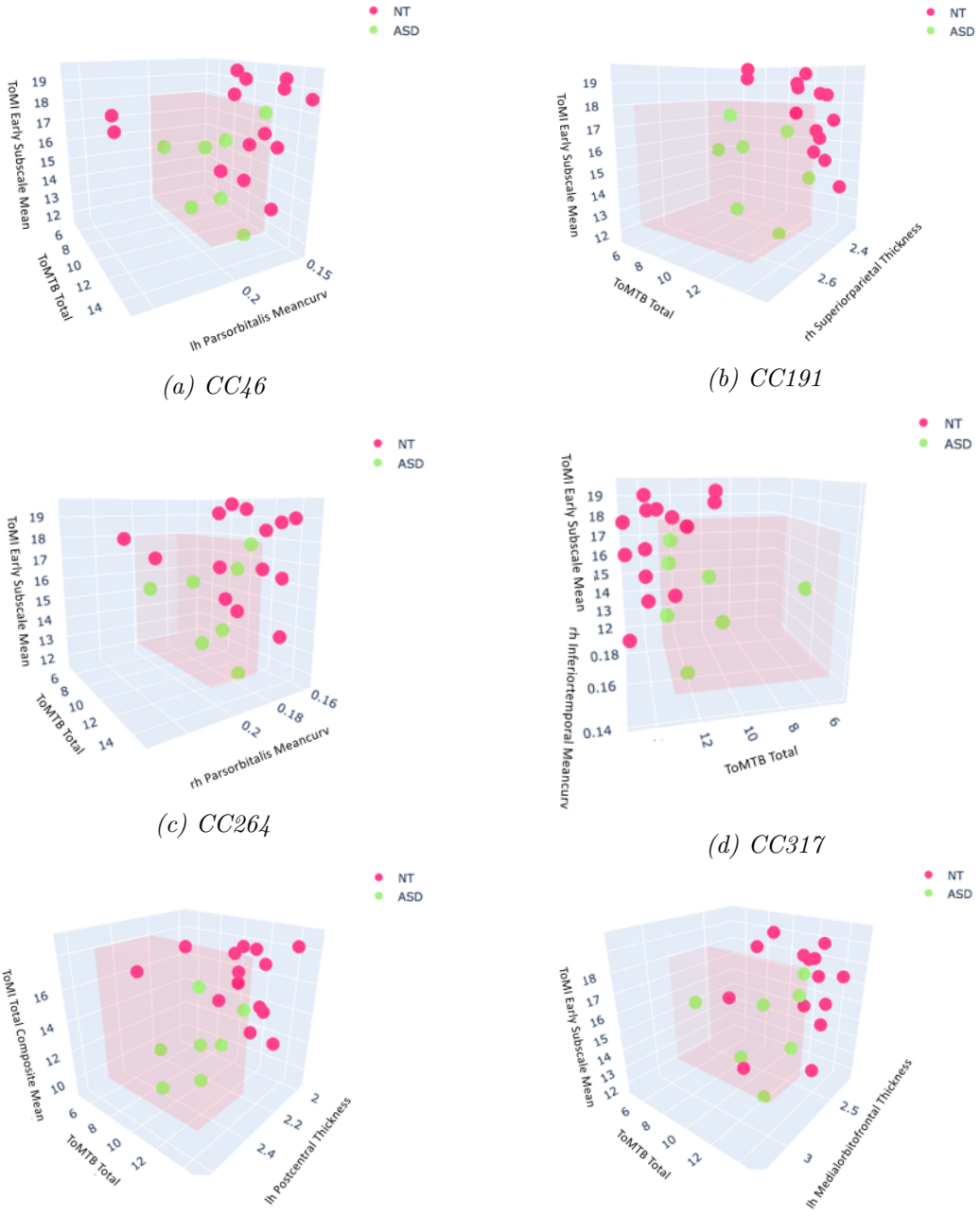
Because of our desire to explore the predictive capability of the behavioral features, we expanded our analysis to include third-order models (i.e., model combinations with three features). There were 651 third-order models in total; while some consisted only of anatomical brain features, others included two behavioral features plus one brain anatomical feature. We selected the 6 best-performing third-order models with the highest fitness (PMF); each had 100% PPV and 100% class coverage, see Table 3.4. Each of these third-order models contained two behavioral features and one brain anatomical feature.

Table 3.4: Third-order CC model features and range of values

CC#	Feature One	Value	Feature Two	Value	Feature Three	Value
46	ToMTB total	[5, 13]	ToMI early subscale mean	[12, 18]	lh parsorbitalis meancurv	[0.17, 0.2]
191	ToMTB total	[5, 13]	ToMI early subscale mean	[12, 18]	rh superiorparietal thickness	[2.4, 2.7]
264	ToMTB total	[5, 13]	ToMI early subscale mean	[12, 18]	rh parsorbitalis meancurv	[0.18, 0.2]
317	ToMTB total	[5, 13]	ToMI early subscale mean	[12, 18]	rh inferiortemporal meancurv	[0.15, 0.18]
1163	ToMTB total	[5, 13]	ToMI total composite mean	[9, 18]	lh postcentral thickness	[2.2, 2.5]
1446	ToMTB total	[5, 13]	ToMI early subscale mean	[12, 18]	lh medialorbitofrontal thickness	[2.6, 2.8]

Using CC 46 (Table 3.4) as an example, any subject who had a total score on ToMTB within the range of 5 to 13 AND an early subscale mean score on ToMI-2 within the range of 12 to 18 AND a mean curvature value of the left hemisphere pars orbitalis within the range of 0.17 to 2 would be classified as having ASD. The ToMTB total score feature occurred in all of our best-fit, third-order models; and the ToMI-2 early subscale mean score occurred in all but one (CC 1163) of the models, where the ToMI-2 total composite mean played a role. Such a finding further suggests that the

ToMTB and ToMI-2 might be effective for ASD testing and diagnosis. See Figure 3.2.



(a) CC46 *(b) CC191*

(c) CC264 *(d) CC317*

(e) CC1163 *(f) CC1446*

Figure 3.2: 3D visualization of third-order CC models.

Green dots represent ASD subjects and group together within the pink cube defining the range of values in Table 3.4

3.3.2 KNN Leave-One-Out Cross Validation

As mentioned earlier, a cohort of new subjects comprising 2 ASD and 5 NT children were enrolled at a later time. This later cohort was combined with the 21 subjects used in CCEA to cross-validate the KNN classifiers.

Using the 8 unique features of the second-order model, the KNN (k=3) achieved 89.29% classification accuracy, where 17 of the 19 NT subjects and 8 of the 9 ASD were classified accurately. See Table 3.5, diagonals of the second-order confusion matrix.

Using the 9 unique features of the third-order model, the KNN (k=7) validation accuracy fell to 78.57% compared to when using the 8 unique features from the second-order model, where 15 of the 19 NT and 7 of the 9 ASD subjects were classified accurately. See Table 3.5, diagonals of third-order confusion matrix.

Given the better ASD classification performance of the second-order neuroanatomical features, and that the behavioral measurements/features are relatively easier to collect among children with ASD, it was important to explore whether the ASD prediction results might be improved when the behavioral features were combined with the second-order features. As a result, we added the three behavioral features (i.e., ToMTB total score, ToMI-2 total composite mean and ToMI-2 early subscale mean) from the third-order models to the 8 second-order brain anatomical features and cross-validated a new KNN (k=2) classifier. With the total of 11 unique features, a validation accuracy of 85.71% was achieved with 16 of the 19 NT subjects and 8 of the 9 ASD being classified accurately. See the confusion matrix of Table 3.5.

Table 3.5: Cross Validation Confusion Matrices

N=28 (9 ASD & 19 NT)	Second-order Model Features		Third-order Model Features		Second-order Model Features Plus Three Behavioral Features	
	Predicted ASD	Predicted NT	Predicted ASD	Predicted NT	Predicted ASD	Predicted NT
True ASD	8	1	7	2	8	1
True NT	2	17	4	15	3	16

3.3.3 Classification of ASD and NT subjects using the KNN model

To further examine whether the KNN classifier could discriminate subjects with ASD and NT, we developed three classification models – one using the 8 unique features from the second-order models, one using the 9 features from the third-order models, and one using the 11-feature model (i.e., eight second-order neuroanatomical features and three behavioral features). The best classification accuracy was achieved using a balanced training set that consisted of 6 NT and 6 ASD subjects, among which only 2 of the 6 ASD subjects were not part of the original CCEA feature selection. The remaining 16 subjects were used for testing (13 NT and 3 ASD).

The KNN (k=1) results for the second-order model features are shown in Table 3.6, columns 2 and 3; a classification accuracy of 87.5% was achieved, with all 3 of the ASD subjects and 11 of the 13 NT being classified accurately. Both of the misclassified NT subjects were part of the original CCEA feature selection.

The KNN (k=3) classification accuracy for the third-order model features was 81.25%, with all 3 of the ASD subjects and 10 of the 13 NT subjects correctly classi-

fied. Of the 3 misclassified NT subjects, 2 were included in the original CCEA feature selection. See Table 3.6, columns 4 and 5.

Lastly, the KNN (k=3) predictions for the combined 11-feature model (8 neuroanatomical features and three behavioral features) are shown in Table 3.6, columns 6 and 7; classification accuracy is 93.75%, with all 3 of the ASD subjects and 12 out of 13 NT subjects classified accurately. The one misclassified NT subject was not part of the original CCEA feature selection analysis.

Table 3.6: Classification Confusion Matrices

N=16 (3 ASD & 13 NT)	Second-order Model Features		Third-order Model Features		Second-order Model Features Plus Three Behavioral Features	
	Predicted ASD	Predicted NT	Predicted ASD	Predicted NT	Predicted ASD	Predicted NT
True ASD	3	0	3	0	3	0
True NT	2	11	3	10	1	12

3.4 Discussion

This study used a new ML feature selection tool, the CCEA, to identify biomarkers and behavioral features capable of successfully discriminating between children (7 to 14 year of age) with and without ASD given a small dataset collected from a single research site. ML tools have long been applied to ASD research; but it remains a far-reaching goal to build a diagnostic system for ASD that incorporates both feature selection and prediction. Previous studies face the challenge of using datasets across different research sites for classification purposes, rather than identifying input

variables most closely associated with ASD (i.e., feature selection) [39, 59, 61, 62, 68, 81, 107, 140, 170, 204, 288]. Additionally, traditional ML algorithms do not work well with ASD datasets given the large amount of variance and the heterogeneous nature of the disorder [127, 148]. Meanwhile, it requires a tremendous amount of effort to include ASD individuals in a research study given the social, cognitive and language challenges of such a population. Thus, nearly all ASD datasets have a large number of features with relatively small sample sizes, which despite being unsuitable for many ML algorithms, often leads to overfitting and poor classification accuracy. However, the CCEA in this work is able to address such issues by efficiently exploring large search spaces for feature interactions associated with some nominal outcome (e.g., ASD or NT). It also adopts built-in tools to prevent overfitting to produce parsimonious models.

The present study demonstrated exceptionally good performance (i.e., 100% ASD PPV and 100% class coverage) of the features identified by the CCEA. The selected CCEA features from the parsimonious second and third order models included volume, area, cortical thickness, and mean curvature in specific regions around the cingulate cortex, frontal cortex, and temporal-parietal junction areas as biomarkers for ASD (e.g., the pericalcarine cortex, posterior cingulate cortex, isthmus of the cingulate gyrus, pars orbitalis, etc.). Such findings are consistent with previous literature suggesting that individuals with ASD have abnormalities in these brain regions [7, 45, 78, 81, 123, 163, 197, 201, 219, 246, 266, 270, 290]. Additionally, third-order models from the training set include measurements from the ToMI-2 and the ToMTB as important features [133, 166], which further validates the use of these tools in ASD assessments.

It is impressive that the KNN classifiers are able to achieve such high classification accuracy given our sample size, and validation of the discriminant features selected by the CCEA models. In particular, the KNN classifiers perform better using the second-order neuroanatomical features than the third-order feature models, which emphasizes the importance of focusing on parsimonious models selected by the CCEA. In addition, the KNN achieved the highest classification accuracy when adding the behavioral features from the third-order models to the neuroanatomical features from the second-order models. In most cases, neuroimaging measurements are conducted along with behavioral assessments together. As the third-order models are included to explore the potential role that behavioral features might play along the side of neuroanatomical features, it is convincing to see the highest classification accuracy are achieved when combining the behavioral features and the neuroanatomical features. These findings highlight the heterogeneous and multi-facet characteristics of ASD itself. Although it is more difficult to implement MRI among children with ASD, such findings support the idea that neuroanatomical measurements increase confidence in diagnosis. It also suggests that a good ASD prediction model should consider including both behavioral and neuroanatomical features.

This study further demonstrates the robustness of the CCEA as a feature selection methodology. The accuracy of these features when used as input variables in the KNN classifier suggest their potential to help clinicians and researchers target specific domains in ToM in treating the social challenges most often seen in children with ASD. More importantly, CCEA is able to capture accurate characteristics of heterogeneous datasets exceptionally well. With the rapid development of "easy-to-use" neuroimaging techniques, CCEA has great potential to assist clinicians in identifying

those individuals who may not be at risk for ASD, hence, shortening the wait-list for diagnosing those with higher risk in need of immediate intervention. The implications of our findings for clinical researchers reinforce earlier findings regarding the brain-behavior connections for children with and without ASD related to ToM understanding [21, 131, 143, 166, 205, 256]. Knowing these connections may guide future researchers in the assessment of change following intervention at both a behavioral and neurobiological level. This may also lead to knowledge about which interventions may be most effective for children with specific neurobiological markers.

The present study has established important biomarker candidates of ASD. These biomarker candidates support previous research adopting traditional neuroimaging measurements identifying similar brain regions to explain the abnormalities in ASD [7, 45, 78, 81, 123, 163, 201, 246, 266, 270]. Importantly, ML methodologies can perform as well as the traditional approaches in the field of neuroscience and specifically in our assessment of ASD in selecting neuroanatomical biomarkers. Although ML techniques have been adopted to help with diagnosis and treatment development in medicine [3, 74, 89, 243], the heterogeneity in ASD creates challenges. Typically, large, diverse, and comprehensive datasets are required to extract solid biomarkers, which can be time-consuming and may be less accurate with traditional approaches. Under such circumstances, ML techniques as described in this study can help advance the development of an automatic diagnostic and predictive system for ASD. The present study provides a new direction for adopting ML techniques in ASD research and other areas of medicine with similar heterogeneity in disease condition.

Chapter 4

Conclusion and Future Direction

Currently available behavioral tests of ToM typical examine one or just a few aspects of ToM; however, the two behavioral tests used in the current study, ToMI-2 [131] and ToMTB [134] are multi-faceted tools that cover several aspects of ToM (e.g., emotion recognition, false belief, perspective taking etc.), including information from both parent and the child.

Two novel ToM tasks were developed for this study that can be used as brain measures of ToM in children. The fToM task was designed to closely resemble an item on the ToMTB, which directly assesses a child's understanding of a series of scenarios tapping ToM. It allowed a direct examination of the correlation between behavioral performance and brain activation patterns associated with ToM (i.e., desire-based emotion). This was the first time a behavioral ToM task was recreated in an fMRI task for comparison of specific emotions in children with ASD. The fER task was designed to assess surprise and embarrassment that are two later developing and more complex emotions requiring ToM. Although there is a plethora of research examining emotion recognition in children with ASD, much of the previous literature examined

recognition of basic emotions such as happiness, sadness, anger, and fear; few studies have examined surprise and embarrassment, and none have investigated the brain areas underlying recognition of these emotions among children with ASD.

All three emotions targeted in the current study are critical aspects of ToM. Surprise and embarrassment are particularly difficult for children with ASD to recognize [121, 132, 265]. While desire-based emotions are easier for children with ASD to recognize, their understanding of these emotions is delicate and often requires explicit descriptions [14, 132, 198, 214, 216, 278, 291]. Further, embarrassment has been studied at a neural level only among adults with ASD [124, 125, 136]; surprise and desire-based emotions have only been examined at a behavioral level in ASD subjects and little is known about their neural correlates. Thus, the studies presented here filled a notable gap in the literature by examining these three emotions from a neuroscience perspective among children with ASD. The current studies were the first to examine the neural correlates of these emotions requiring ToM and establish the connections between behavior and brain activities in children with ASD (i.e., 7 to 14 years old). Specifically, the first manuscript, *A Pilot Study Using Two Novel fMRI Tasks: Understanding Theory of Mind and Emotion Recognition Among Children With ASD*, investigated the neural mechanisms involved in two specific aspects of ToM: the recognition of basic and "complex" emotions (i.e., surprise, embarrassment), and the understanding of desire-based emotions. Building upon findings from previous studies, the study provided a deeper and more systematic understanding of the brain-behavior connections associated with ToM leading to an increased understanding of the brain regions involved in ToM. With this knowledge, intervention research can be developed that supports brain-behavior connections leading to nor-

malized social performance. Such brain-behavior research might also help predict those brain-behavior profiles of children that will most likely to benefit from specific ToM or social cognitive based interventions. This is important as causal modeling in ASD suggests that interventions need to be delivered at the cognitive level to bridge behavior with brain function [128]. Further, brain and behavioral characteristics can be combined with new machine learning (ML) methods to build prediction models to help detect ASD, and select important biomarkers of ASD population to achieve personalized interventions.

Due to the heterogeneous nature and early onset of ASD, detection and diagnosis of ASD often require significant time and costs. Early diagnosis of ASD is crucial for early intervention so that it can emphasize strategies to address the core social impairment in autism. A time efficient, low cost, and accurate system to facilitate the diagnosis of ASD will help determine whether a child needs further assessment, which will save both human and financial resources, as well as speed up the diagnostic process. As an effort to build automatic diagnostic tools for ASD, science has progressed significantly to classify ASD individuals from NT individuals using ML approaches. However, challenges in classification performance remain due to data variance introduced via scanner hardware, imaging protocols, operator characteristics, regional demographics, and other site-specific acquisition factors. In addition, most studies in the field focus on classification and prediction rather than discriminant feature selections in ASD. In the second manuscript, *Identifying Neuroanatomical and Behavioral Features for Autism Spectrum Disorder Diagnosis in Children using Machine Learning*, a conjunctive clause evolutionary algorithm (CCEA) was adopted to identify biomarkers and behavioral features capable of successfully discriminating

between children (i.e., 7 to 14 year of age) with and without ASD, given a small dataset collected from a single research site. This was the first study to successfully introduce a novel evolutionary algorithm (i.e., CCEA), which identified both behavioral and neuroanatomical biomarkers associated with ASD. More importantly, the algorithm prevented overfitting and demonstrated robust classification performance with a small sample size. It provided evidence that ML techniques can be applied effectively in ASD research and other areas of medicine with similar heterogeneity in disease condition.

This dissertation work is part of a larger study examining the behavioral and neural changes surrounding ToM and emotion recognition following a nine-week social cognitive intervention (i.e., Social Stories) designed to improve social functioning in children with ASD. Social Stories™(SSs) facilitate the ToM of children with ASD by reading short stories individually developed based on a child's successful and/or unsuccessful social experiences [154,159,196]. A unique aspect of this intervention is the ability to emphasize specific instances of emotion recognition and understanding as well as other aspects of ToM that may be a specific target for a child with ASD. In the ongoing larger study, SSs are designed following parental discussion of actual social situations in which a child had difficulty or was successful in understanding surprise, embarrassment, and desire-based emotion. SSs have been shown to enhance children's social understandings and address challenging behaviors [154, 159, 196]. They have also been shown to improve ToM, in part due to their focus on emotion recognition, making them especially promising for children with ASD in whom ToM deficits contribute to impairments in perceiving and interpreting other's emotions [236].

Research on interventions to improve social cognition and overall life skills is

consistently endorsed as an aspirational research priority in surveys of the ASD community. The larger study in which this novel dissertation work was developed is an effort to optimize a treatment program that improves social functioning to ultimately reduce the economic and social burden of care for individuals with ASD in the future. Knowing children with ASD can engage in fMRI tasks as well as behavioral tasks so that brain-behavior connections can be made is an important contribution of this dissertation work. The development of two fMRI measures that assess ToM and are aligned with behavioral measure of ToM is another major contribution to researchers working to better understand the brain areas involved in ToM and ultimately ASD. These contributions should help facilitate the development of individualized treatment recommendations and refine how interventions are implemented. This dissertation work also supports additional efforts to determine the differential effects of other interventions (e.g., Comic Strip Conversations [129, 130]), including the great potential to apply ML techniques to explore and define ASD subtypes that may benefit from specific interventions.

In summary, this dissertation work will contribute to our understanding of the neural mechanisms underlying ToM related emotion recognition and important neural anatomical and behavioral biomarkers in ASD. By building such brain-behavior connections, it will promote the development of more accurate and efficient assessment tools and treatment methods. In addition, it will advance the application of ML in ASD and neuroscience research to achieve automated predictive and diagnostic models.

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