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White Matter Integrity, Facial Emotion Perception, and Socialization in Autism Spectrum Disorders

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WHITE MATTER INTEGRITY, FACIAL EMOTION PERCEPTION, AND SOCIALIZATION IN AUTISM SPECTRUM DISORDERS

by

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Under the Direction of Tricia Z. King

ABSTRACT

Difficulty interpreting facial expressions is an important component of social deficits seen in Autism Spectrum Disorders (ASDs). The amygdalo-fusiform white matter tract is theorized to contribute to facial expression interpretation. The current study examined relationships between white matter integrity (WMI) along the aymgdalo-fusiform pathway, facial emotion perception (FEP), and socialization skill (SS) in a sample of typically developing (TD) participants and participants with ASDs. Groups were differentiated by WMI along the amygdalo-fusiform tract. Results suggested unexpected negative relationships between WMI and SS, and between WMI and FEP in the ASD group. A group interaction was suggested for WMI and FEP such that participants with ASDs demonstrated a negative relationship, whereas TD participants displayed the hypothesized positive relationship. Overall, findings suggest that measures of WMI along the amygdalo-fusiform tract should not be conceptualized identically in participants with ASDs and controls.

INDEX WORDS: White matter integrity, Facial emotion perception, Socialization skill, Autism spectrum disorders

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INTRODUCTION

Autism Spectrum Disorders (ASDs) are a class of increasingly prevalent and pervasive neurodevelopmental disorders that affect an average of 1 in 88 children born in the United States (CDC, 2012). The autism spectrum includes the diagnoses of Autistic Disorder, Asperger Syndrome, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). These disorders are characterized by deficits in social function (primarily reciprocal social interaction), communication, and the presence of repetitive stereotypic behaviors (American Psychiatric Association, 2000).

Difficulties resulting from these disorders have a strong negative effect on quality of life for individuals diagnosed with ASDs and their families (Kuhlthau et al., 2010; Lee, Harrington, Louie, & Newschaffer, 2008; Shu, 2009). ASDs also present heavy financial burdens for affected groups. Recent studies have estimated that the lifetime cost to care for an individual diagnosed with an ASD is nearly $3.2 million dollars when direct (behavioral interventions and additional care) and indirect (lost productivity) costs are considered (Ganz, 2007).

Social Deficits in ASDs

Since the diagnostic label of autism was first coined by Kanner (1943), a deficit in social functioning has been repeatedly highlighted as one of the autism spectrum's most distinctive features (Gillham, Carter, Volkmar, & Sparrow, 2000; Loveland et al., 1997; Rogers, 2000). In contrast, similar difficulties with communication can be found in primary language disorders. Individuals diagnosed with intellectual disabilities also can share the repetitive behaviors and restricted interests common in individuals diagnosed with autism (Bodfish, Symons, Parker, & Lewis, 2000; Petty, Allen, & Oliver, 2009). Difficulties in social functioning however, are generally unique to ASDs (Schultz, 2005).

The social deficits apparent in autism spectrum disorders have been the subject of a considerable body of research. In many cases, a focus on understanding how social deficits manifest are motivated by a theory that these deficits are some of the earliest and most important symptoms to emerge. Prominent research groups have proposed models that highlight early deficits in social functioning as key factors contributing to later difficulties for individuals diagnosed with ASDs (Klin, Jones, Schultz, & Volkmar, 2003; Mundy & Neal, 2000). These developmental perspectives theorize that the early social deficits in developing children with ASDs negatively impact their ability to develop other essential skills including the ability to communicate effectively early in life.

It has been suggested that the social deficits in autism could be "superordinate", or the first of the three major deficits to emerge and capable of moderating or explaining the emergence of other ASD symptoms, though links to repetitive behaviors are less robust (Schultz, 2005) than links to communication deficits. Studies have found that children identified as having early difficulties with social reciprocity later evidence atypical development of early communicative abilities (Alessandri, Mundy, & Tuchman, 2005; Klin et al., 2003; Mundy & Crowson, 1997; Siller & Sigman, 2002). Multiple theories have been proposed to explain factors underlying social impairments in individuals diagnosed with ASDs, though the specific source of this deficit remains unclear.

Some researchers argue that a weakness in the ability to innately infer the feelings, intents, and perceptions of others, or theory of mind (Premack & Woodruff, 1978) is related to social functioning deficits in ASDs. If an individual is unable to understand that others might have a different mind-state in a given situation, understanding another person's social perspective may be difficult or impossible (Baron-Cohen & Corcoran, 1995). Though there has

been some evidence to suggest that the theory of mind deficit is not present in all forms of ASD, the type and difficulty level of the task used to determine this deficit may play a role in differing results (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997). The theory of mind deficits in ASDs also have been linked to differences in gaze patterns between ASD and control participants (Akechi et al., 2009; Kuhn et al., 2010; Stauder, Bosch, & Nuij, 2010; Young, Merin, Rogers, & Ozonoff, 2009) and differences in the ability to empathize with others (Besel & Yuille, 2010; Smith, 2009) across age groups. Others propose a weakness in the ability to integrate the multiple sources of detailed information essential to understanding and appropriately reacting to stimuli during interaction due to a more detail oriented cognitive approach (Happé & Frith, 2006).

Socialization skills in ASDs

One method that has been used to quantify the severity of social deficits in participants is the measure of socialization skill. Socialization is the process through which an individual adequately and appropriately interacts with others in the social environment, comparable to others his/her same age (Preis, 2007). For both typically developing (TD) individuals and those affected by ASDs, socialization is of critical importance as it is one of the primary means for building meaningful social relationships and satisfying the basic human need of belonging (Wilhite, Tripp, Smith Canter, & Floyd, 2009). As socialization skill, specifically proficiency in social interactions, relationships, and conversation is an essential component of everyday functioning, measures focusing on adaptive functioning commonly include a socialization subscale. Adaptive functioning is a measure of the effectiveness with which a person can perform activities necessary to meet the everyday demands of life and utilize skills essential for daily living (Sparrow, 2005).

Deficits in socialization skills also serve as an effective marker to differentiate ASDs from other developmental disorders. Researchers using the Vineland Adaptive Behavior Scales (Sparrow, 2005), a common measure of adaptive functioning featuring socialization, communication, and daily living skill subscales, found that participants with ASDs typically display relatively strong daily living skills, mild impairments in communication, but have significant deficits in socialization skills (Carter et al., 1998; Liss et al., 2001). This relatively unique pattern of adaptive functioning skills could assist in differential diagnosis of an ASD.

One study predicted adaptive behavior scores on the Vineland Adaptive Behavior Scales based on the mental age of three groups of the participants diagnosed with Autism, PDD-NOS (Pervasive Developmental Disorder-Not Otherwise Specified), and other developmental disorders (DD) (Gillham et al., 2000). These scores were compared to actual adaptive functioning scores in this same sample of children. Participant scores in the Autism group on the Socialization Scale were lower than other groups and significantly lower than the level predicted by participant chronological age and mental age. Delays in socialization skills were most strongly related to diagnosis and accounted for 48% of the variance in diagnosis. Ratios of actual socialization scores vs. socialization scores predicted by chorological age correctly classified 86% of autism and nonautism (PDD-NOS and DD) cases.

Another study used socialization skill in combination with other social measures in an effort to better define subgroups with ASD in a sample of children with Fragile X Syndrome (Budimirovic et al., 2006). The combination of socialization skills and social withdrawal was useful in differentiating a subgroup of boys with both ASD and Fragile X Syndrome diagnoses from a group of boys with only Fragile X Syndrome diagnoses across time points. Specifically,

emotion recognition abilities and verbal labeling of emotions were most predictive of ASD status in this sample.

These studies demonstrate that measures of socialization skill are particularly sensitive in identifying participants with ASD symptomatology. As treatments for developmental disorders can vary considerably, and these disorders can be difficult to distinguish (especially in early stages), there is a need for additional research focused on clarifying the specific mechanisms involved in the expression of these deficits in individuals affected by ASDs. Socialization skills serve as a possible avenue for greater specificity in distinguishing the presence of ASD symptomatology in groups of participants with developmental disorders. Further studies aimed at identifying core factors relating to differing levels of socialization skill can help researchers and clinicians better define the social profile unique to Autism Spectrum Disorders.

Facial emotion perception in ASDs

While there are many factors that may contribute to social difficulties for individuals with ASDs, weaknesses in processes aiding the appropriate perception of emotion have been continually suggested in the literature. Emotion perception is the ability to correctly recognize and interpret an emotional experience (Newman & Lorenz, 2003). As there are few sources of emotional information more rich than human facial expressions, facial processing tasks are among the most widely used methods for studying emotion perception in participants affected by ASDs (Jemel, Mottron, & Dawson, 2006).

There is a wealth of results from studies using facial perception stimuli to test for deficits in this population. It is very important however, to separate findings featuring facial emotion recognition and facial identity recognition. Whereas both abilities are related to recognizing key features of human faces, facial emotion recognition tasks test the ability to interpret which facial

emotion (and accompanying emotional state) can be attributed to a specific configuration of movements on a face. Facial identity recognition involves the skill to determine if the features of an object are recognized as a face and if that face has been seen before. Though facial identity is an important skill that may play a role in the social difficulties in ASD's, a relatively weak association between facial recognition skill and socialization skill has been previously suggested (Klin et al., 1999). Therefore, the present study is focused on facial emotion recognition. When it is considered that accurately judging facial emotions is an integral part of everyday human interaction, it is clear that a weakness in the ability to interpret facial emotions would have a strong negative impact an individual's ability to interact with others in a social context.

There is considerable variability in results from studies concerned with determining facial emotion recognition abilities in individuals diagnosed with ASDs. Participants with ASDs have been shown to be slower and/or less accurate than controls in these tasks with a variety of static (still images) and dynamic (short video clips) stimuli requiring participants to label faces with emotions including (but not limited to) happy, sad, angry, fearful, and disgust (Ashwin, Ricciardelli, & Baron-Cohen, 2009; Bal et al., 2010; Celani, Battacchi, & Arcidiacono, 1999; Dziobek, Bahnemann, Convit, & Heekeren, 2010; Gross, 2004; Grossman & Klin, 2000; Law Smith, Montagne, Perrett, Gill, & Gallagher, 2010; Wright et al., 2008). In one study, participants with ASDs evidenced greater difficulty than controls in understanding static and dynamic facial emotions expressed by others without voice cues, even when emotion labels were provided for them (Lindner & Rosén, 2006).

Other studies have found that participants with ASDs do not evidence poorer performance on basic facial emotion recognition tasks than controls on tasks that use dynamic facial emotion stimuli (Gepner, Deruelle, & Grynfeltt, 2001; Loveland et al., 1997) or static

facial emotion stimuli (Adolphs, 1999; Hubert, Wicker, Monfardini, & Deruelle, 2009; Neumann, Spezio, Piven, & Adolphs, 2006; Robel et al., 2004; Rosset et al., 2008).

Even in studies where differences in facial emotion recognition accuracy between ASD and TD groups were not found, subtle differences between each group's approach to the task were detected. For example, when facial emotion stimuli included voice cues, ASD participants performed at similar levels to controls, suggesting that this additional information allowed ASD participants to compensate for emotion recognition difficulties (Lindner & Rosén, 2006). Decreased visual attention to the upper quadrant of the face (determined by gaze pattern) and physiological responses differing from controls (Hubert et al., 2009) have also been determined in participants affected by ASDs.

It has been repeatedly suggested that variability in findings from facial emotion recognition studies could be due to differences in demographics (participant age and IQ) and task demands as some stimuli allow higher functioning participants to compensate with cognitive, verbal, or perceptual compensatory strategies (Harms, Martin, & Wallace, 2010). Specific ASD diagnosis also has been considered a factor as the majority of studies on facial emotion perception in ASDs only include high functioning ASD participants (as opposed to participants with more impaired abilities on the more severe end of the spectrum) due to task demands. However, as all ASD diagnoses are theorized to share a core social deficit, it has been suggested that differences in the diagnostic composition of samples should not play a large role in variable findings (Harms et al., 2010).

A recent study examined emotion perception as a potential mediator in the relationship between diagnostic group and the individual scales from a measure of adaptive functioning (Hudepohl, Robins, King, & Henrich, 2009). Emotion perception measured by the Diagnostic

Analysis of Nonverbal Accuracy-Second Edition (DANVA-2; Nowicki, 2004) partially mediated the relationship between diagnostic group (typically developing participants and individuals diagnosed with ASDs) and two scales of the Vineland Adaptive Behavior Scales, Second Edition (VABS-II): Socialization and Daily Living Skills (Hudepohl et al., 2009). The strongest indirect effect was found on socialization skill. This model suggests that impaired emotion perception abilities in individuals with ASDs may play an important role in explaining lower levels of socialization skill in ASD groups.

fMRI Studies of Facial Emotion Perception in ASDs

Functional Magnetic Resonance Imaging (fMRI) allows researchers to identify differing levels of activation within specific regions of the brain. Efforts to determine activation patterns related to facial emotion perception in TD and ASD-affected samples have identified several key areas that play important roles in accurate facial emotion perception. In ASD samples, some of the most common findings include the hypoactivation of the amygdala (Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007; Baron-Cohen et al., 2000; Schultz, 2000) and fusiform gyrus (Corbett et al., 2009; Critchley et al., 2000; Greimel et al., 2010; Hubl et al., 2003; Schultz, 2000; Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004) on facial perception tasks.

Activation of the amygdala is commonly correlated to tasks including social and emotional perception, whereas activation in the fusiform gyrus (specifically in the Fusiform Face Area [FFA] region) is commonly related to more invariant aspects of the face including identity (Harms et al., 2010; Schultz, 2005). The FFA region is also commonly thought to be related to distinguishing characteristics of objects with which an individual is particularly familiar (Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999). Early development of facial perception

and social skills has been hypothesized to be supported by an amygdala–fusiform system (Schultz, 2005) and the concerted efforts of both of these regions has been described as crucial for emotional face processing (Dziobek et al., 2010).

Some studies focused on brain region activation during facial perception tasks find results in areas outside of these regions above (Pierce, Muller, Ambrose, Allen, & Courchesne, 2001; Pierce & Redcay, 2008). The region around the superior temporal sulcus (STS) has also been studied as a region important in facial emotion processing (Baron-Cohen et al., 1999; Haxby, Hoffman, & Gobbini, 2000; Pierce et al., 2001; Robins, Hunyadi, & Schultz, 2009). Activation in this area is commonly considered to be related to the perception and integration of more variable aspects of the face including gaze, facial expression, and auditory cues (Harms et al., 2010; Robins et al., 2009; Schultz, 2005). It has been suggested that variability in these results may evidence abnormal connectivity between multiple brain structures (Verhoeven, De Cock, Lagae, & Sunaert, 2010).

Diffusion Tensor Imaging

Diffusion Tensor Imaging (DTI) is an emerging technique utilizing structural data collected in vivo during MRI scans. DTI enables researchers to examine brain region connectivity through visualization of water diffusion speed and path through brain tissue. This method of visualization presents an exciting opportunity for researchers to study the quality of white matter connections between key regions of the brain and has been successfully employed to study multiple diseases and disorders (Mori & van Zijl, 2002). DTI yields several measures useful in determining differences in white matter integrity. White matter integrity is generally described as a measure of the structural properties of white matter fiber tract connections in the brain. By examining how water molecules flow along these paths, an approximation of white

matter quality, or how well the fibers conduct information between areas of the brain can be constructed. Low white matter integrity has been theorized to contribute to reduced communication between important areas of the brain, leading to varying levels of dysfunction.

Fractional Anisotropy (FA) and Mean Diffusivity (MD) are two common measures of white matter integrity. Fractional Anisotropy (FA) is a directional measure of the organization (size, myelination and density) of white matter fibers (Basser & Pierpaoli, 1996). Higher FA values have been described as an indication of increased white matter quality. Mean Diffusivity (MD) yields an overall measure of diffusion in through the brain tissue. Increases in MD have been related to neurological insult and brain disease as a gross measure of tissue structure integrity (Miles et al., 2008; Thivard et al., 2007; Wozniak et al., 2006). This measure is a more general indicator of diffusion across tissue and lacks the directional information included in FA.

While FA and MD are commonly cited as measures of white matter quality, microstructural differences indicated by individual components of these measures can also be determined. Diffusion can be measured in three directions along the axes of white matter fibers. Axial Diffusivity (AD) quantifies diffusion parallel to the direction in which the bundle is oriented towards. The remaining two directions quantify diffusion perpendicular to AD and each other (Noriuchi et al., 2010). The average of diffusion measured along these two directions is called Radial Diffusivity (RD). Decreased AD and increased RD have been suggested as indications of lower white matter quality, whereas increased AD has been suggested to reflect higher white matter quality (Budde et al., 2008; Nagesh et al., 2008).

DTI studies of emotion perception in ASDs

Building upon findings from fMRI studies identifying activation in regions of the brain involved in emotion processing; research utilizing Diffusion Tensor Imaging (DTI) data has

emerged to describe differences in white matter in regions identified as important to this process (see Table 1). This approach allows for an opportunity to "connect the dots" previously identified; both defining neural systems related to facial emotion perception and yielding information about how differences in the quality of these connections influence this process.

The first study utilizing an exploratory whole-brain analysis using DTI with participants diagnosed with ASDs found lower FA values at multiple points in the brain when ASD participants were compared to typically developing control participants (Barnea-Goraly et al., 2004). Of particular importance to the present study, reduced FA values also were found in the amygdala and fusiform gyrus, bilaterally. The disruptions were discussed as possible underlying factors in impairments in cognitive functioning, abnormal responses to sensory stimuli, and difficulties processing social information.

A later study by Keller et al. (2007) determined lower FA values within the corpus callosum and right side posterior portions of the internal capsule for ASD-affected participants. These results were suggested to be related to difficulties integrating multiple sources of information in these participants. The possibility of reduced synchronized activation in brain regions resulting from lower quality white matter connections were suggested as factors in social symptoms in ASDs, including theory of mind deficits. A recent study examining white matter structure in young participants (mean age 3.2 years) diagnosed with ASDs also found reduced FA values in the corpus callosum and additional microstructural white matter abnormalities along the superior longitudinal fasciculus and cingulum (Weinstein et al., 2011). Similar to the work of Keller et al., results related abnormal connectivity between major brain regions to core deficits commonly found in ASDs.

The work of Sundaram et al. (2008) focused specifically on examining white matter connections within the frontal lobe in an ASD-affected sample. Decreased FA and increases in an apparent diffusion coefficient (ADC), a measure similar to MD, were found in the frontal lobe for ASD participants. This study interpreted these findings as evidence of abnormal white matter tract organization in ASD-affected participants. Ke et al. (2009) also identified significantly lower FA values in the frontal lobe for participants diagnosed with ASDs.

Contrasting results were found in the work of Cheng et al. (2010). This DTI study found significantly increased FA in the frontal lobe and along with additional brain regions in an ASD sample. An age by group interaction was noted in the superior frontal gyrus and paracentral lobule such that FA decreased as age increased in ASD participants, while FA increased as age increased in control participants. These findings support the frontal disconnectivity theory of autism, an area of the ASD literature that highlights abnormalities in frontal cortex connectivity observed during development that could be related to the manifestation of ASD symptomatology. It is hypothesized that individuals diagnosed with ASDs undergo an early period of accelerated white matter growth soon after birth, followed by a period of decelerated white matter development later in life compared to TD children (Courchesne, Carper, & Akshoomoff, 2003). Contrasting FA values in frontal regions between studies could be explained by age differences between study samples.

Noriuchi et. al (2010) found lower FA and AD for ASD-affected participants in the amygdala, corpus callosum, and additional brain regions. Lower FA in the left dorsolateral prefrontal cortex was correlated with social impairment, and white matter abnormalities around the amygdala, superior temporal sulcus, and other regions related to social cognition were highlighted. Another study found increased RD (along with other microstructural differences)

around the superior temporal gyrus and temporal stem when ASD and control groups are compared (Lee et al., 2007).

Chueng et. al. (2009) found significantly lower FA in their ASD-affected sample in prefrontal and temporal regions near the fusiform gyrus. Higher ASD symptomatology was correlated to lower FA in these regions. Specifically, difficulties with social reciprocity and communication were correlated with lower FA along frontal and temporal paths, while repetitive behaviors correlated with abnormalities found in the corpus callosum, splenium, and cerebellum. Increased FA was determined in the right inferior frontal gyrus and left occipital lobe. These findings were interpreted as evidence supporting higher activation and compensatory reorganization of white matter in this region resulting from increased reliance on non-verbal, and lower–order visual analysis determined by a previous study (Koshino et al., 2005).

Most relevant to the current study, DTI data was used to demonstrate a previously unexplored white matter pathway between the amygdala and fusiform gyrus (and hippocampus and fusiform gyrus) in a mixed ASD and TD sample by Conturo (2008), and later replicated in a typically developing sample by Smith (2009). Though this pathway had been hypothesized by indirect methods in previous studies in the ASD literature (Dziobek et al., 2010; Schultz, 2005), DTI allowed for more concrete structural evidence to support the connection between these regions. The importance of microstructural white matter characteristics along this pathway was highlighted.

Whereas the pathways were of similar size and shape between ASD and control groups, the connection between the amygdala and fusiform gyrus demonstrated increased AD and RD Conturo et al. (2008). These findings were suggested as indications of combined myelination decrease and axonal loss in white matter between these areas. The authors proposed these results

are evidence that whereas the general pathway "machinery" between the amygdala and fusiform gyrus is in place in the ASD group, microstructural and behavioral findings provide evidence that the machinery is operating abnormally Conturo et al. (2008). Lower RD values between the hippocampus and amygdala were correlated with lower facial identity recognition scores in ASD participants, a reversal of the expected relationship. It was suggested that these varied results are evidence of a unique pathologic processes in ASD participants along these pathways.

Table 1. DTI Study Summary

Study	Participants	DTI Findings for ASD Participants
Barnea-Goraly, et al. (2004)	7 ASD (AR: 13.4±2.8), 9 TD (AR: 14.6±3.4), Age, gender, and IQ matched	Decreased FA: ventromedial prefrontal area, interior cingulate gyrate, temporoparietal junctions, superior temporal sulcus, temporal lobe, occipitotemporal tracts, corpus callosum, adjacent to amygdala and fusiform gyrus
Keller et al. (2007)	34 ASD (AR: 18.9±7.3), 31 TD (AR: 18.9±6.2), Age matched	Decreased FA: in the posterior midbody corpus callosum, left anterior corona radiata, right anterior corona radiata, forceps minor, right retrolenticular internal capsule
Weinstein et al. (2011)	22 ASD (AR: 3.2±1.1), 32 TD (AR: 3.4±1.3), Not matched	Increased FA: midbody of corpus callosum, left cingulum
Sundaram et al. (2008)	50 ASD (AR: 4.8±2.4), 16 TD (AR: 6.8±3.5), Not matched	Decreased FA: frontal lobe: short range fibers Increased MD: frontal lobe: frontal fibers, long range fibers

Ke et al. (2009)	12 ASD (AR: 8.8±2.3), 10 TD (AR: 9.4±2.1), Age and gender matched	Decreased FA: frontal lobe, left temporal lobe, right anterior cingulated, superior temporal sulcus,
Cheng et al. (2010)	25 ASD (AR: 14±4), 25 TD (AR: 14.5±3.5), Age and IQ matched	Decreased FA: right posterior limb of internal capsule, right paracentral lobule, bilateral superior frontal gyrus Increased FA: frontal lobe, right cingulate gyrus, bilateral insula, right temporal gyrus, middle cerebellar peduncle middle
Noriuchi et al. (2010)	7 ASD (AR: 14±2.7), 7 TD (AR: 13.4±2.7), Age and gender matched	Increased FA: left dorsolateral prefrontal cortex (correlated with social impairment), superior temporal sulcus, right temporal pole, amygdala, superior longitudinal fasciculus, occipitofrontal fasciculus, left corpus callosum, right cingulate
Lee et al. (2007)	43 ASD (AR: 16.2±6.7), 34 TD (AR: 16.4±6.0), Age and gender matched	Decreased FA: superior temporal gyrus (bilaterally), temporal stem (bilaterally).
Cheung et al. (2009)	14 ASD (AR: 10±4), 14 TD (AR: 10±4), Age matched participants	Decreased FA: bilateral prefrontal lobes, area near fusiform gyrus Increased FA: right inferior frontal gyrus, left occipital lobe, right superior frontal longitudinal fasciculus, left occipital lobe
Conturo et al. (2008)	17 ASD (AR: 35.5±17.9), 17 TD (AR: 34.1±17.6), Age, gender, ethnicity, IQ matched	Increased RD and AD: between amygdala and fusiform gyrus (bilaterally) Decreased RD: between amygdala and hippocampus in right hemisphere.

Smith et al. (2009)	15 TD (AR: 27.5±9.1),	Amygdalo-fusiform path determined in Conturo et al. (2008) replicated in TD sample.

Note: ASD- participants with autism spectrum disorders
TD- typically developing participants
AR- age range in years
FA- fractional anisotropy (increases typically considered better quality white matter)
MD- mean diffusivity (increases typically considered lower quality white matter)
AD- axial diffusivity (increases typically considered better quality white matter)
RD- radial diffusivity (increases typically considered lower quality white matter)

The Current Study

Previous studies have recommended that future work should focus on differences in structural connectivity and how deficits relate to socio-emotional deficits in ASDs (Bal et al., 2010; Conturo et al., 2008; Dziobek et al., 2010; Harms et al., 2010; C. Smith et al., 2009). A key consideration for further study in this area is the role of abnormal facial emotion recognition in the core social deficits inherent in ASDs. It is possible that difficulties in facial emotion perception could be a cause, effect, or modifying factor of these deficits (Harms et al., 2010; Leppänen & Nelson, 2006). Further study is required to examine this relationship in the context of structural connectivity differences in individuals diagnosed with ASDs.

In an effort to expand upon the findings previously described in Hudepohl et al. (2009), the current study proposes a method by which the relationships between white matter differences, emotion perception, and socialization skill can be examined together in a mixed sample of ASD-affected and TD participants. Whereas there has been a recent increase in studies examining differences in white matter pathways in individuals diagnosed with ASDs and a more established body of research focusing on facial emotion perception and socialization

skills in this population; the current study is the first time known to the authors that all three factors have been examined concurrently.

The proposed study will examine the relationship between the white matter amygdalo-fusiform pathway in the right hemisphere (Figure 1), emotion perception, and socialization skills in a combined group of individuals with ASDs and typically developing participants. The study's purpose is to determine if a concurrent examination of these relationships could provide a more complete picture of a possible biological mechanism underlying socialization difficulties in a combined sample of participants with ASD and typically developing participants.

Specific Aims

Aim One of the study is to determine if group differences between TD participants and participants diagnosed with ASDs can be established based on the integrity of the white matter connections between the amygdala and fusiform gyrus. The outcome of this (and all measures in the study) will be heavily influenced by small sample sizes and accompanying low statistical power. As differences will need to be extreme to satisfy the requirements for a significant difference between groups, effect sizes will also be presented.

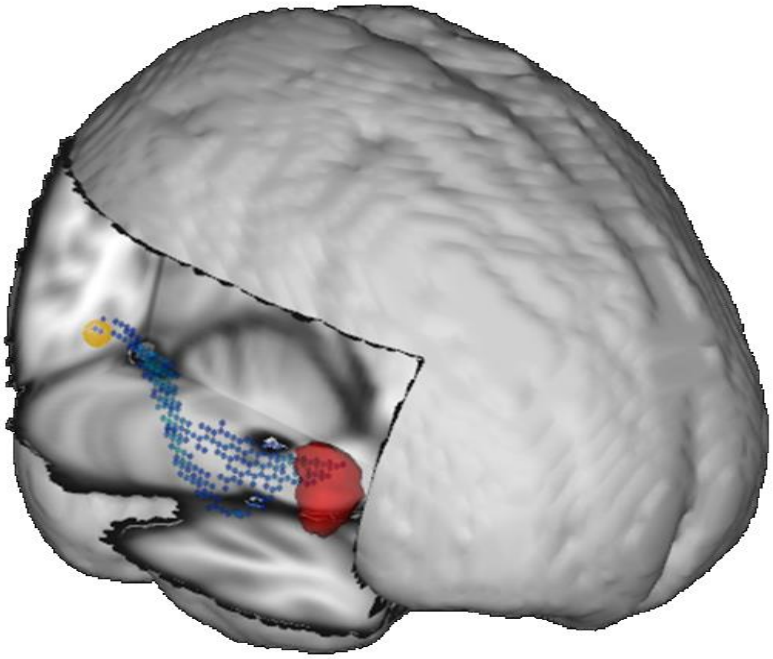

Figure 1. Amygdalo-Fusiform tract from current study participant

Aim Two of this study is to establish relationships between white matter integrity along the amygdalo-fusifom tract, facial emotion perception, and socialization skill. White matter integrity between the amygdala and the hypothesized location of the fusiform face area was measured with white matter tractography as employed by Conturo (2008) and Smith (2009). It is hypothesized that FA will correlate positively with measures of facial emotion perception and socialization skill in the overall sample such that, as FA increases, scores on both the measures of facial emotion perception and socialization skill will increase. It is also hypothesized that MD will correlate negatively with measures of facial emotion perception and socialization skill in the overall sample such that, as MD increases, scores on both measures of facial emotion perception and socialization skill will decrease.

FA and MD values were also calculated along a control tract (the right corticospinal tract) for all participants per recommendations from previous studies (A. Kumar et al., 2010; Walsh et al., 2011). It is hypothesized that relationships determined between FA and MD along the

amygdalo-fusiform tract, facial emotion perception, and socialization skill will not be replicated with FA or MD values along the corticospinal tract. This finding will help reinforce results determined along the target tract as specific to the amygdalo-fusiform tract and not simply due to overall white matter differences.

Aim Three is to investigate emotion perception as a mediator of the relationship between white matter integrity and a measure of socialization skill in the ASD sample (Figure 1). It is hypothesized that emotion perception will partially mediate the relationship between white matter integrity and socialization skill. If the proposed study can find evidence of a reliable neurophysiological marker along the amygdalo-fusiform pathway with differences that correspond to differences in emotion perception and socialization within the mixed sample; this research would contribute to the body of knowledge defining ASD's unclear etiology. These findings also may contribute to more effective diagnosis and treatment strategies for individuals diagnosed with ASDs.

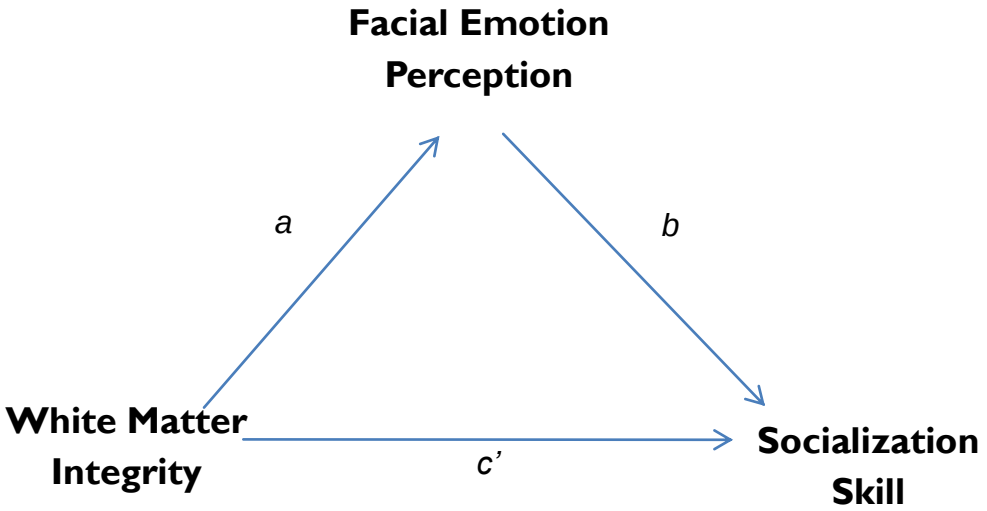

Figure 2. Proposed mediation model

METHOD

Participants

Participants in the current study were selected from a larger project investigating psychophysiological correlates to facial emotional processing in Autism Spectrum Disorders (co-PI's: King & Robins). Participants in the parent study were recruited from clinic referrals, community organizations, local autism societies and the undergraduate research pool at Georgia State University. This study was approved by both the Georgia State University (where assessments were conducted) and the Emory University Biomedical Imaging Technology Center (where MRI data were collected) institutional review boards. Consent and assent were obtained from all participants and guardians.

Exclusion Criteria and Resulting Sample Demographics

All participants with IQ scores determined by the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) as below 70 or MRI scans with significant artifact were excluded. Control participants were excluded if they had scale elevations consistent with ASD symptomatology on the Social Communication Questionnaire (SCQ; Rutter et al., 2003), impaired emotion perception abilities based on below average performance on the Benton Facial Recognition Test (BRT; Benton et al., 1983), the Diagnostic Analysis of Nonverbal Accuracy-Second Edition (DANVA; Nowicki, 2004), and clinically significant elevations on the Behavior Assessment System for Children-Second Edition (BASC-2; Reynolds & Kamphaus, 2004). Additionally, controls with previously diagnosed neurological insult, co-morbid psychological disorder and/or or learning disability could not participate in the study. Inclusion criteria for ASD group participants included meeting criteria for autism on the Autism Diagnostic Interview-Revised (ADI-R; Le Couteur et al., 2003) and an ASD on the Autism Diagnostic Observation

Schedule (ADOS; Lord et al., 1999). In order to participate in the present study, participants could not present with any present or past neurological abnormality or brain injury.

Five control participants and four participants with ASDs were excluded from the study due to missing VABS-2 and DANVA-2 scores. Two control participants and 4 participants with ASDs were excluded due to missing structural and/or diffusion imaging data. Two control participants and 1 participant with an ASD diagnosis were excluded due to significant motion artifact in diffusion imaging volumes. Four control participants with significant elevations (T-scores greater than 70) on the BASC-2 subscales of Inattention, Depression, Hyperactivity, and Conduct Problems were excluded from final analyses. One ASD participant also was excluded due to a WASI Full Scale IQ (FSIQ) that fell below 70. Based upon all exclusion criteria, a total of 14 control participants and 8 participants with ASDs from the original study sample of 44 were excluded from final analyses.

The ASD group has 5 males and 3 females with ages ranging from 10 to 23 years of age at visit time (M=15.42, SD=4.66). The ASD sample included 87% Caucasian and 12% African American participants. Within the TD group there were 9 males and 5 females ranging from 9 to 19 years of age at visit time (M=13.78, SD=3.43). The TD sample included 64% Caucasian, 14% African American participants, and 22% participants who did not report an ethnicity. Demographic variables are displayed in Table 2. No significant group differences between age ($t(20)= -0.95$, p=.35), sex ($\chi^2(1, N = 22) = 0.01$, p = .93), ethnicity ($\chi^2(1, N = 22) = 2.10$, p = .55), or FSIQ ($t(20)= 0.38$, p=.71) were determined.

Table 2. Descriptive Statistics for Full Sample

	ASD (n=8)	TD (n=14)	Group Difference
Age Mean Years (SD) **Age Range**	15.42 (4.66) 10-23	13.78 (3.43) 9-19	NS
% Female	37.50	40.00	NS
Ethnicity Count (Caucasian/ Non-Caucasian)	7/1	9/5	NS
WASI FSIQ (SD) **WASI FSIQ Range**	105.88 (17.92) 83-129	108.43 (13.60) 78-128	NS

Note: WASI FSIQ =Wechsler Abbreviated Scale of Intelligence Full Scale IQ; NS= Not Significant

Subsample

To match the sample size of each group and determine if any group relationships were obscured by the influence of the larger control sample, parallel analyses to those described above were carried out with an a subsample of 8 typically developing participants and 8 participants diagnosed with ASDs. Subsample demographics are reported in Table 3. Results from the smaller sample are reported below when parallel analyses differ from the larger sample.

Table 3. Descriptive Statistics for Subsample

	ASD (n=8)	TD (n=8)	Group Difference
Age Mean Years (SD) **Age Range**	15.42 (4.66) 10-23	14.73 (3.61) 10-19	NS
% Female	37.50	37.50	NS
Ethnicity Count (Caucasian/ Non-Caucasian)	7/1	5/3	NS
WASI FSIQ (SD) **WASI FSIQ Range**	105.88 (17.92) 83-129	111.88 (13.10) 83-123	NS

Note: WASI FSIQ =Wechsler Abbreviated Scale of Intelligence Full Scale IQ; NS= Not Significant

Measures

Socialization Skill

To measure the construct of socialization skill, the Survey Interview form of the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) was collected from participant caregivers. This measure of adaptive behavior is divided into Socialization, Daily Living Skills, and Communication scales. The VABS-II also yields an overall measure of adaptive function as an Adaptive Behavior Composite score (Sparrow et al., 2005).

This measure features a large age range and is therefore well suited for use with the wide range of ages in the present study sample. The VABS-II has been employed across multiple settings and studies to assess socialization skill in individuals with ASD diagnosis (Carter et al., 1998; Liss et al., 2001; Paul et al., 2004). Clinical samples tested for validity with this measure included a sample of 46 individuals aged 3 to 19 years. The mean socialization scale score for this group was found to be two standard deviations below the mean socialization score in the reference group. The VABS-II has shown also good discriminatory validity between diagnostic categories (Sparrow et al. 2005) and has been used in multiple studies to assess socialization skill in diverse samples. As the focus of this study will be on socialization behaviors, only response on the Socialization subscale will be considered. The Socialization subscale yielded a test-retest reliability of .76 in a normative sample of 90, with 14 to 21 year old typically developing participants.

Emotion Perception

In order to measure the construct of emotion perception, all participants were presented with the Diagnostic Analysis of Nonverbal Accuracy (DANVA-2). This measure employs 4 subtests: Adult Paralanguage, Child Paralanguage, Adult Facial Expressions and Child Facial

Expressions, each with 24 stimuli (Nowicki, 2004). Subtests are administered by a computer in a randomly generated order. As the present study is mostly concerned with facial emotion perception, only participant responses on the Child and Adult Facial Expressions subtests will be analyzed. In the Adult and Child Facial Expressions subtests, the participant must assign one of 4 emotion labels (happy, sad, angry, and fearful) and an emotion degree (high or low) to a color image of an actor's facial expression (Nowicki & Duke, 1994, 2001).

The DANVA-2 was selected for the current study as it one of the few emotion perception tests to allow for separate scales for both adults and children. The DANVA-2 Adult and Child facial expressions subtest stimuli also consist of still photos. This helps eliminate possible confounds from concurrent audio stimuli and dynamic facial movement. The DANVA-2 also features multicultural male, female, child and adult, actors for facial expression stimuli. This measure has been used to determine nonverbal communication skill in varied clinical and control samples (Spell & Frank, 2000; Sprouse, Hall, Webster, & Bolen, 1998). In ASD samples, the adult faces subtest was found to correlate with a measure of ASD symptomatology (Ingersoll, 2010), though one study found the original DANVA an insufficient tool to distinguish between clinical (PDD-NOS) and control groups on facial emotion perception (Serra, Jackson, van Geert, & Minderaa, 1998). While previous success was not determined with the childhood face subtest the present study employs a combined measure of child and adult faces to better simulate the real-world demands of facial emotion perception.

Though the DANVA-2 was initially designed for use with children, it has been demonstrated to be acceptably reliable with older participants. Coefficient alphas ranged from .64 (first grade students) to .77 (college age students) for the Adult Facial Expressions subtest and .70 (first grade students) to .74 (college age students) were determined for the Child Facial

Expressions subtest (Nowicki & Carton, 2001). Test-retest reliabilities for these subtests were also acceptable, ranging from .73 to .93.

ASD Symptomatology

Participants from the larger study sample diagnosed with an ASD were selected for the proposed study. The current "gold standard" for differentiating disorders on the Autism Spectrum, the Autism Diagnostic Observation Schedule (ADOS) was administered to confirm that ASD participants met criteria for a diagnosis. The ADOS is a semi-structured and standardized assessment tool designed to detect deficits in the previously described areas considered in diagnosis of an autistic disorder in individuals suspected of having an ASD (Lord, et al., 1989). While conducting the ADOS, the examiner encourages activities and conversations with the participant in order to observe specific behaviors theorized to be common in individuals with autism spectrum diagnoses. The authors reported good inter-rater reliability estimates on task items (weighted kappas ranging from .61 to .92). Test-retest reliability was also acceptable (weighted kappas ranging from .58 to .92 on general ratings of impairment. Published validity studies also suggest strong predictive validity. Measure sensitivities range from 90% to 97%, and specificities ranging from 87% to 94% for ASD clinical diagnoses (Lord, et al., 2000). The ADOS social interaction total is a subscale of this measure that features a cut-off for social behaviors consistent with Autism. Participants who score below 4 are interpreted as not presenting with behaviors consistent with an ASD and participants who score below 7 are interpret as not presenting with behaviors consistent with Autistic Disorder.

The Autism Diagnostic Interview-Revised (ADI-R) was used in conjunction with the ADOS to confirm ASD diagnoses in the present study sample. The ADI-R is a semi-structured interview measure completed with caregivers of individuals being evaluated for ASD diagnoses

or other developmental delays. The caregiver's description of the individual's early developmental milestones, approaches to communication, play styles, and problem behaviors enable the interviewer in distinguishing symptoms unique to ASD diagnoses. The authors report acceptable inter-rater reliability estimates ranging from .60 to .67 and intraclass correlations ranging from .52 to .97. Test-retest reliability was strong with weighted kappas ranging from .93 and .97 (Rutter et al. 2003). Published validity studies suggest an acceptable level of internal consistency with Alpha coefficients ranging from .54 to .89.

Imaging Technique: Diffusion Tensor Imaging

This study employed Diffusion Tension Imaging (DTI) to determine the quality of white matter connections between specific regions of interest (ROIs) in all participants. This advanced method of structural imaging allows visualization of white matter tract structure and coherence in vivo based on a measure of water diffusion through brain tissue (Barnea-Goraly, et al., 2004). Whereas functional magnetic resonance imaging (fMRI) allows for the identification of what regions of the brain activate during a task relative to a control task, DTI allows investigators an opportunity to identify the direction and quality of white matter pathways between selected brain regions. This technique can yield several quantitative measures.

If white matter pathways are conceptualized as three dimensional bundles of fibers between areas, DTI data can be reduced to three principal eigenvalues (λ_1, λ_2, λ_3) along axes of the bundles. Fractional Anisotropy (FA) and Mean Diffusivity (MD) are two common measures of white matter integrity. Fractional Anisotropy (FA) is a directional measure of the organization (size, myelination and density) of white matter fibers (Basser & Pierpaoli, 1996). Higher FA values have been described as an indication of increased white matter quality. Mean Diffusivity (MD) yields an overall measure of diffusion through the brain tissue. Increases in

MD have been related to neurological insult and brain disease as a gross measure of tissue structure integrity (Miles et al., 2008; Thivard et al., 2007; Wozniak et al., 2006). This measure is a more general indication diffusion across tissue and lacks the directional information included in FA.

White Matter Tractography Preprocessing

White matter tractography is a method that allows for the application of DTI measures to the visualization and analysis of white matter pathways connecting regions of the brain. All MRI image processing tools mentioned below were selected from the FMRIB Software Library (FSL) Diffusion Toolbox (FDT 2.0) to conduct tractography and compute measures of white matter integrity (Smith et al., 2004; Woolrich et al., 2009).

The Brain Extraction Tool (BET) was used to remove non-brain tissue data from structural and diffusion images. Eddy current distortion introduced by standard operation of the scanner and simple head translation during the scan was corrected using the Eddy Current Correction tool. Diffusion tensor imaging model parameters were adjusted to fit each participant's diffusion data volume with FSL DTIFIT software. The BEDPOSTX tool estimated the diffusion parameters for each voxel in each total diffusion volume.

Manually-Defined Region of Interest Selection

Manually-defined regions of interest (ROIs) in the right amygdala and right fusiform gyrus were created for each participant. To aid in the detection of ROI boundaries for the amygdala, the FMRIB's Integrated Registration and Segmentation Tool (FIRST v1.2) was used. The tool created an estimation of the position of the amygdala structure for each participant based on shape models from previous manually segmented images provided by the Center for Morphometric Analysis (CMA) at Massachusetts General Hospital (Patenaude, Smith, Kennedy,

& Jenkinson, 2011). Following this, the right amygdala ROI was manually adjusted to exclude the hippocampus and surrounding tissue for each participant using boundaries defined by previous studies, (Bach, Behrens, Garrido, Weiskopf, & Dolan, 2011; Morey et al., 2009) using the FSL View Tool. To define the fusiform face area, the FSL View Tool was used to draw a region of interest in the right fusiform gyrus most commonly activated during fMRI face processing tasks. Per recommendations from previous studies, the posterior boundary was drawn in the posterior fusiform region on the coronal slice in which the intersection of the parietal-occipital sulcus and the calcerine sulcus was also visible in the sagittal plane. The ROI was drawn in the white and grey matter region defined by the most inferior gurus of the fusiform for 8 slices of tissue in an anterior direction (Onitsuka et al., 2005; Pierce et al., 2001).

Atlas-Defined Region of Interest Selection

To create a standard anatomic definition for the amygdala as suggested by Smith (2009), the Harvard-Oxford Subcortical Structural Atlas was used within the FSL View Tool to automatically select the right amygdala for each subject. As no established anatomical boundaries exist for the fusiform face area, the mean center talairach coordinate point of the fusiform face area activation as determined by previous studies was used and transformed into each subject's individual structural volume space, replicating the method suggested by Smith (2009). To create the suggested 10cm spherical ROI surrounding this point to include white matter in this region for each subject, the FSLMATHS tool was used.

Control Region of Interest Selection

To aid in establishing the specificity of findings along the amygdalo-fusiform tract, a control region was selected along the right corticospinal tract as suggested by previous studies (R. Kumar et al., 2010; Walsh et al., 2011). To anatomically define this control region, the right

corticospinal tract selection mask from the probabilistic John Hopkins University White Matter Tractography Atlas (Hua et al., 2008) was used for all participants.

Probabilistic Tractography and White Matter Integrity Measure Calculation

Probabilistic tractography was used to determine white matter connections between both sets of ROIs. Probabilistic tractography is a measure of structural connectivity which repetitively samples voxel-wise principal diffusion directions to determine to most likely path of a white matter tract. This creates a distribution of the most probable dominant pathway between the regions which attempts to account for uncertainty in individual participant data (Behrens 2007).The PROBTRACKX tool was used to apply a probabilistic tractography algorithm to compute likely white matter connections between each set of ROIs for participant (Behrens et al., 2003).

The resulting tracts were thresholded at 50% with the FSLMATHS tool and converted to MNI standard structural space using the FLIRT tool. Tracts were then overlayed on each the participant's FA and MD specific volume map which also had been converted to standard MNI space. This method allowed for standardized comparisons and a calculation of average FA and MD values between subjects within the regions defined by both manually, atlas-defined, and control white matter tracts with the FSLMEANTS tool.

Procedure

Trained graduate students and/or trained undergraduate students administered behavioral and neuropsychological measures during each session in the Georgia State University Psychology Department. In cases where ASD diagnostic measures were unclear, the PI (Robins) administered and interpreted measures. All participants were presented with both written and spoken explanations of what to expect before each session and signed written informed consents.

Participants were also informed that their participation in the study was completely voluntary and that they could withdraw at any time without penalty. Participants under 18 years old gave written assent along with their legal guardian's written consent. Participants were told that all data collected during the study would remain confidential (barring exceptions otherwise required by law).

Participants were tested individually, and were offered opportunity to take breaks from testing as needed. Task order was counterbalanced across and within measures when possible. Participants were given the option of completing all testing in one session or over two sessions on two dates. In either case, the structural MRI data was collected during an additional session on a 3 Tesla scanner at Emory Medical Center. Participants were informed that MRI scans do not pose any known risks, and carefully screened for any external or internal ferrous material, preexisting conditions, and any other factors that could endanger them during the scan. Trained MRI technicians operated the scanner during data collection and participants were able to communicate with center staff and graduate students while in the scanner. Structural MRI Data was collected as part of a longer MRI scanning session that also included functional imaging. All participants received $50.00 compensation for travel and time spent in the study. All data collected was stored in a de-identified, secure digital database along with data collected as part of the larger, Georgia State University and Emory IRB-approved study.

Planned Analyses

Data were entered into Apache Open Office and Microsoft Excel. All statistical analyses were conducted with SPSS version 14. Given the small sample size in this study, careful attention was applied to descriptive statistics and the distribution of participant scores on each measure in addition to traditional analyses. Scatter plots are provided in the results section

below to illustrate associations between measures. Measures of effect size also are provided for each association. Cohen (2003) suggests a method by which the difference between two effect sizes from independent samples can be tested for statistical significance. This is accomplished through the use of shared standard error between samples and the difference between effect sizes to create a confidence interval. Results from this method are provided below. Z-scores were computed from VABS-II (Sparrow et al., 2005) and DANVA-2 (Nowicki & Duke, 2001) raw scores using respective normative data. In order to include only facial emotion perception scores from the DANVA-2, the absolute value of the mean facial error z-score (comprised of child and adult facial emotion perception error scores) was used.

Power Analyses

A power analysis was conducted to determine the sample size necessary to detect effects of interest. Given the small sample size in the present study, effect sizes will be helpful in identifying relationships that are likely to be statistically significant with a larger number of participants. Power analyses were conducted using G*Power version 3.1.2 (Faul, Erdfelder, Lang, & Buchner, 2007), in which power was set to .80 and alpha was set at .05. In order to detect a medium effect size (.15) with two predictor variables, the ideal sample size for this study was 68 participants. Given the current sample size of 22 participants (14 typically developing and 8 with ASDs), the actual power to detect the desired medium effect size (quantified as R^2) of .15 was .30. As further analyses will be underpowered due to the small samples size, additional information are provided below about data distribution and individual effect sizes for variable relationships.

RESULTS

Preliminary Analyses

Levene's Test for Equality of Variances detected no significant differences in variance between groups on all shared measures analyzed. The distribution of continuous variables was examined for normality through the use of Q-Q and P-P plots. Continuous variables including age, FSIQ, socialization skill, facial emotion perception, and all measures of white matter quality were normally distributed in the sample, allowing for the use of two-tailed Pearson's correlations to determine relationships between the variables. No evidence of multicollinearity (correlation between two variables exceeding 0.80 that leads to sharing and distortion of partial regression coefficients) was determined between independent variables.

Potential Confounds

No significant difference in age was determined between TD and ASD groups. Despite the use of age-standardized measures of VABS-II socialization skill, a strong correlation was determined between age and socialization skill in the ASD group, such that as age increased, socialization skill scores decreased. Given the expected increase in more complex social skills as ages in the normalization sample increase, it is not surprising to find this relationship in the ASD group. Although we do not consider age to be a confound, an exploratory analysis was conducted to determine if further discussion about age effects in this sample was warranted. Age was entered as a predictor in parallel hierarchical regression analyses involving socialization skill. While this reduced the probability that relationships were due to chance for multiple measures within the ASD group, no findings above the alpha of .05 reached statistical significance after controlling for age.

FSIQ and facial emotion perception scores demonstrated strong correlations within the ASD group ($r(7) = .88$, $p < .01$). Correlations between FSIQ and socialization skill scores were similarly strong within the ASD group ($r(7) = .77$, $p = .03$). As FSIQ increased, so did both facial emotion perception scores and socialization skill scores. Per Dennis's recommendations (2009), FSIQ was not considered as a valid covariate within the ASD sample. However, previous studies have suggested that participants diagnosed with ASDs can recruit cognitive resources to assist them in performing better on emotion perception tasks than their peers (Harms et al., 2010). To determine if this finding was replicated in the current sample, FSIQ was entered as a predictor in parallel hierarchical regression analyses involving socialization skill and facial emotion perception as dependents. No findings above the alpha of .05 reached significance after controlling for FSIQ.

Aim 1: Establishing group differences based on white matter quality

As hypothesized in Aim 1 above, an independent samples t-test detected a significant group difference based on mean FA value along the manually-defined white matter tracts connecting the amygdala and fusiform face area. As noted in Table 4, participants with ASDs had significantly lower mean FA (M=.338, SD=.05) than typically developing participants (M=.379, SD=.07, $t(20)$= 2.29, p=.03). Figure 3 features a bar graph illustrating group differences. The effect for this difference was calculated as Cohen's d= .96; a very large effect size (Cohen, 1988). A parallel t-test using FA values determined through the atlas-based method did not establish significant differences between participants with ASDs (M=.36, SD=.09) and typically developing participants (M=.38, SD=.07, $t(20)$= .64, p=.53). The effect for this difference was calculated as Cohen's d= .25.

Independent samples t-tests also were conducted to determine group differences on all other measures. A significant difference was detected on VABS-II socialization skill, where participants with ASDs had significantly lower scores (*M*=-2.11, *SD*=1.60) than TD participants (*M*=.45, *SD*=.92, *t*(20)= 4.80, *p*<.01), as expected given the literature. In contrast with expectations given the literature, no significant difference was detected between groups on the combined measure of child and adult facial emotion perception from the DANVA-2. This is likely the result of the restricted range of responses (all within normal limits) for both TD and ASD group participants. In addition, no group differences could be determined between measurements of average MD along the amygdalo-fusiform tract.

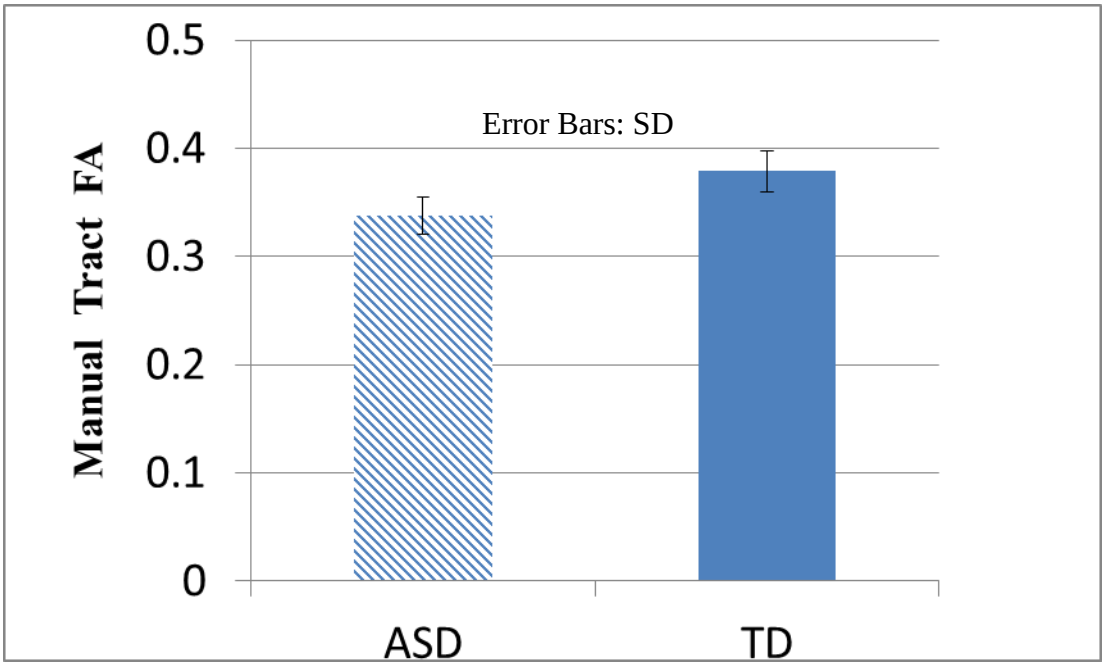

Figure 3. Amygdalo-fusiform mean fractional anisotropy

In the subsample of 16 participants (8 in each group), group differences could not be determined based on white matter quality values, although a trend was revealed such that participants with ASDs (*M*=.34, *SD*=.05) had lower FA scores along the amygdalo-fusiform tract than TD participants (*M*=-.38, *SD*=.04, *t*(14)= 1.91, *p*=.08). However, the effect size for this difference

was large with Cohen's *d* calculated as .95. This large effect size was similar to that found for the same comparison within the larger group.

Of note, no significant group differences could be determined between FA or MD values along the control tract (the right corticospinal tract).

Table 4. Group Differences

	ASD Group Mean (SD)	TD Group Mean (SD)	p	Effect Size	% Impaired* (ASD,TD)
Socialization Skill	-2.11(1.60)	0.45(0.92)	<.001	d=1.96	75%,0%
Facial Emotion Perception	0.05(0.53)	0.03(0.44)	NS	d=0.04	0%,0%
Manual Tract FA	0.34(.05)	0.38(0.03)	.033	d=0.97	
Atlas Tract FA	0.36(0.09)	0.38(0.07)	.NS	d=0.25	
Manual Tract MD	0.09(0.01)	0.09(0.01)	NS	d=0.02	
Atlas Tract MD	0.08(0.01)	0.08(0.01)	NS	d=0.20	
Control Tract FA	0.52(.09)	0.55(.05)	NS	d=0.41	
Control Tract MD	0.09(.02)	0.08(.01)	NS	d=0.46	

Note: df for all comparisons=20; NS=Not Significant; Socialization Skill= Vineland-2 Socialization domain z-score; Facial Emotion Perception=z-score created from value of mean DANVA-II Adult Faces and Child Faces scores multiplied by -1; FA=fractional anisotropy; MD=mean diffusivity (all scores x100); *=impaired defined as z-scores of -1.5 or lower

Aim 2: Relationships between Amygdalo-Fusiform Tract White Matter Integrity, Facial Emotion Perception, and Socialization Skill

Path c': The Relationship between FA and Socialization Skill

In order to test the hypothesis of significant relationships between variables presented in the hypothesized mediation model (Figure 2), two-way Pearson's correlations were conducted. The relationship between FA along the white matter pathways bridging the manually-defined amygdala and fusiform face area with socialization skill (path c') was not significant within the

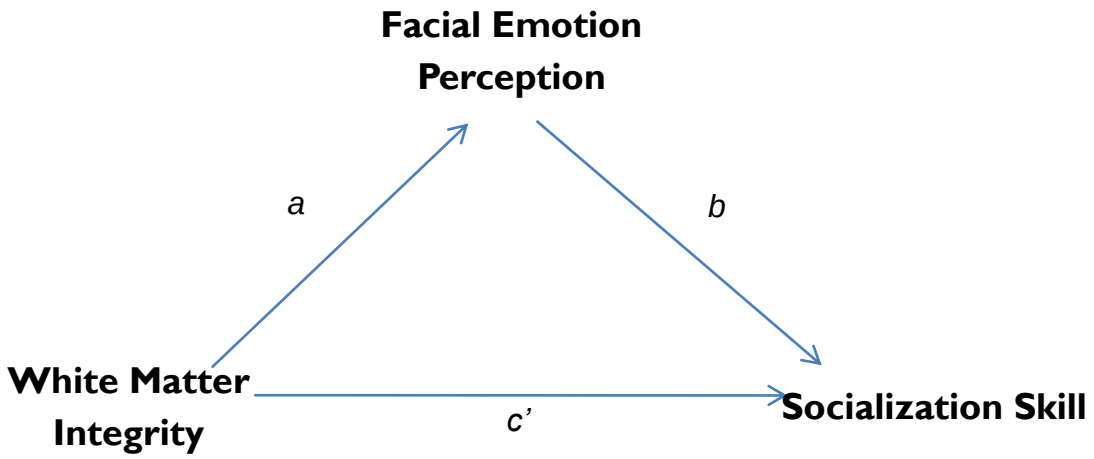

Figure 2. Proposed mediation model

overall sample ($r(20)= .09$, $p= .70$) or within TD ($r(12) = -.50$, $p= .07$) or ASD groups ($r(6) =-.35$, $p = .40$). However, a scatterplot of these variables (Figure 4) reveals potentially interesting relationships when groups are examined separately. The association between the amygdalo–fusiform tract FA and socialization skill shows a similarly negative slope (as FA increases, socialization skill decreases), for both groups.

Tract FA accounted for less than 1% of the variance in socialization skill within the mixed group (R^2=.01, p=.70). Within the ASD group, tract FA accounted for 12% of the variance (R^2=.12, p=.40), whereas 24% of the variance in socialization skill was accounted for by tract FA in the TD group (R^2=.24, p=.07), a notable trend. Employing Cohen's method (2003) yielded a confidence interval for the difference between the group R^2's that included zero ($CI_{.95}$ = -1.46, 1.69), indicating that the difference between groups was not significant at the alpha=.05 level.

Path c': Atlas-Defined Approach Findings

When a correlation between an atlas-defined pathway and socialization skill was conducted with the same participants, a similar (though less pronounced) pattern emerged. Whereas no significant relationships were determined within the overall sample or TD and ASD groups, a slightly negative slope emerges for both groups when they are examined separately.

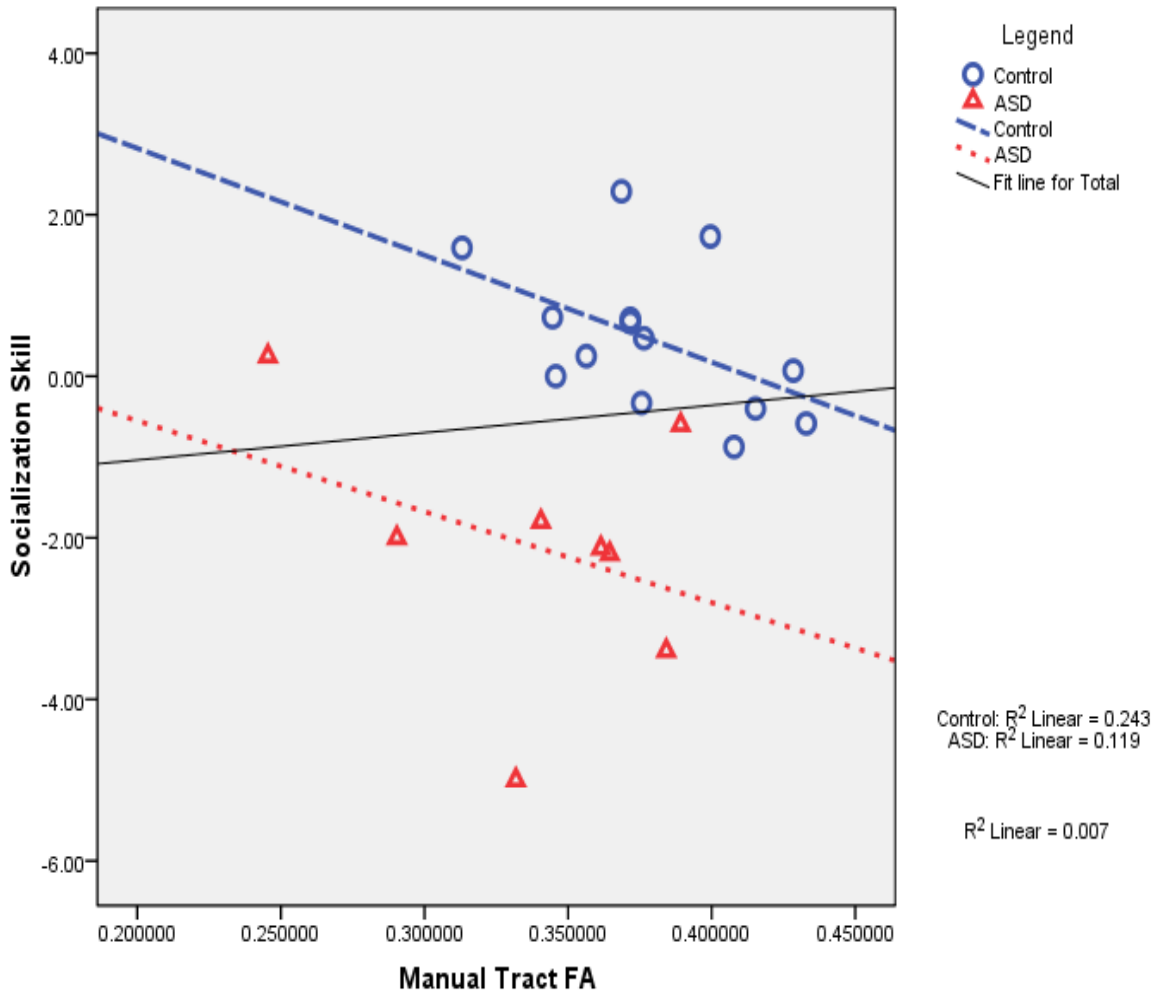

Figure 4. Relationship between manual tract fractional anisotropy and socialization skill

Lower effect sizes than those determined with the manually-defined approach were observed for nearly all relationships examined with the Atlas-defined (Figure 5). Atlas-defined

tract FA accounted for less than 1% of the variance in socialization skill within the mixed group (R^2<.01, p=.87). Within the TD group, 2% of the variance in socialization skill was accounted for by tract FA (R^2<.02, p=.62). White matter along the tract defined by atlas-based ROIs accounted for 7% of the variance in socialization skill for the ASD group (R^2<.07, p=.53). The method defined by Cohen to detect significant differences between effect sizes yielded a confidence interval for the difference between the group $R^{2'}$s that included zero ($CI_{.95}$ = -1.85, 2.70), indicating that this difference was not significant at the alpha=.05 level.

Path c': The Relationships between Mean Diffusivity and Socialization Skill

Correlations were conducted to test relationships between MD along manual tracts, facial emotion perception, and socialization skill. As tract MD for both TD and ASD groups increased, socialization skill increased. Similar to data distributions for FA values, this was the opposite of the expected direction. Whereas the correlation between tract MD and socialization skill was not significant, tract MD explained 32% of the variance in socialization skill for the ASD group (R^2=.32, p=.16)

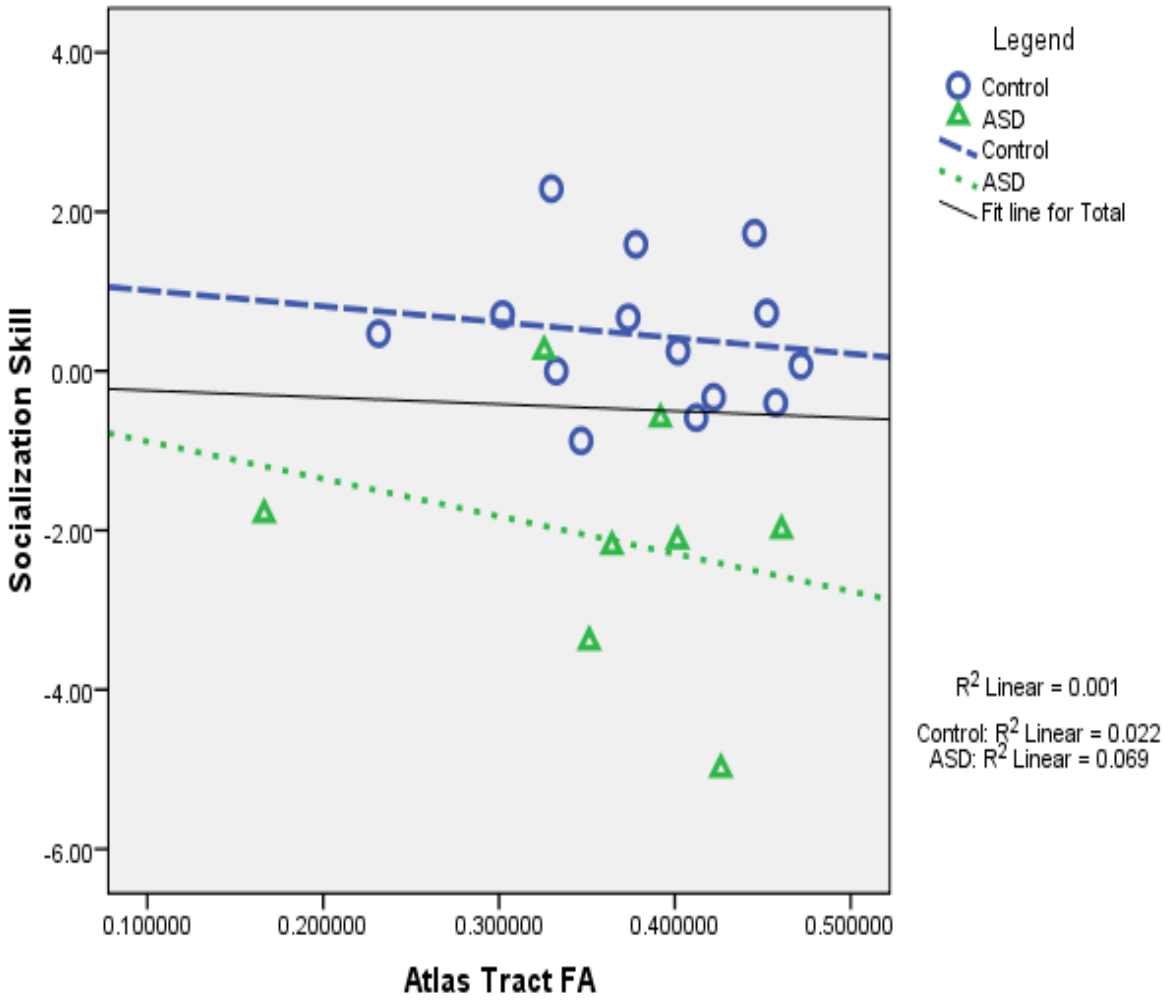

Figure 5. Relationship between atlas tract fractional anisotropy and socialization skill

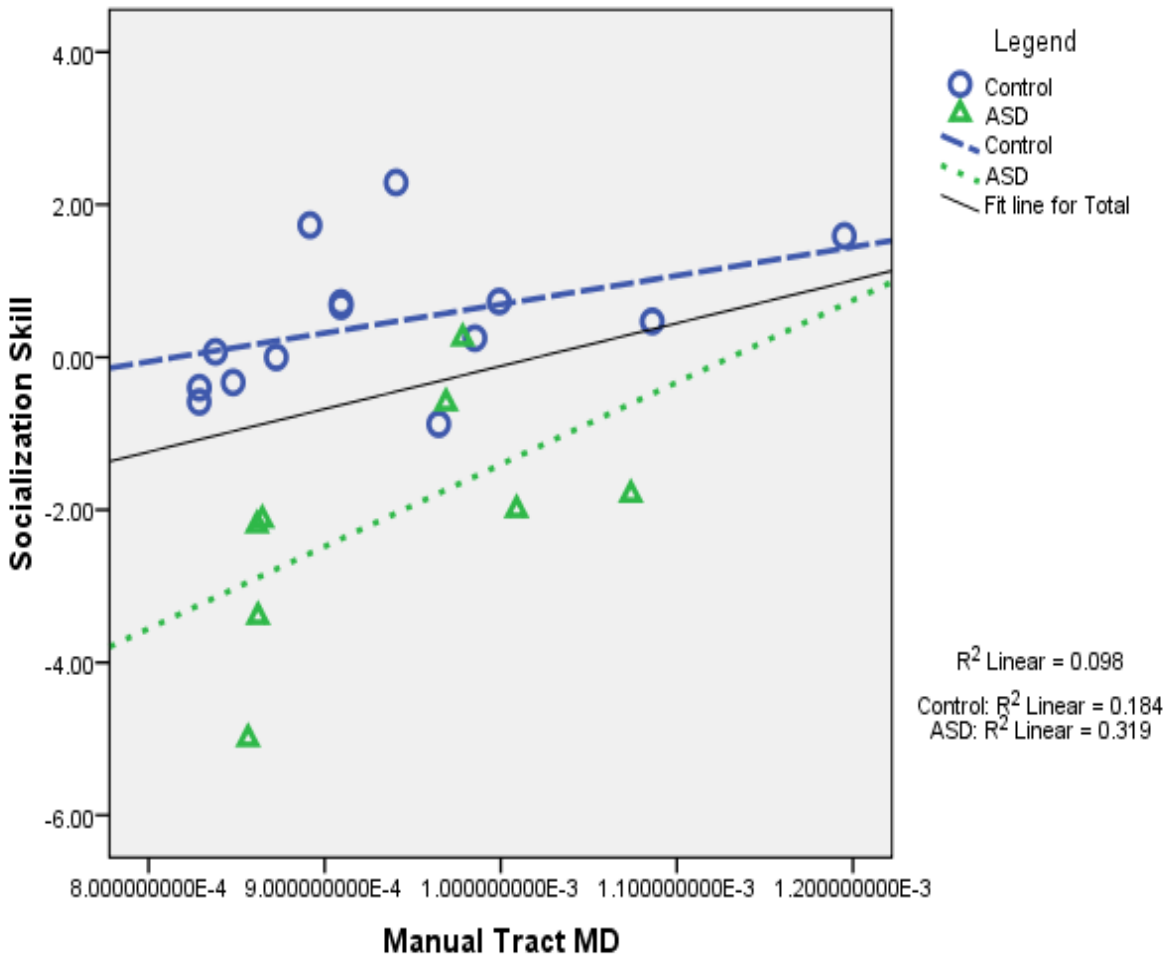

Figure 6. Relationship between manual tract mean diffusivity and socialization skill

This was a notably larger effect size than was explained by FA for participants with ASDs in the same analysis (Figure 6). When the same relationship was examined using atlas-defined tract MD, no notable relationships are observed. Cohen's method yielded a confidence interval for the difference between the group $R^{2'}$s that included zero ($CI_{.95}$ = -1.38, 1.65), indicating that this difference was not significant at the alpha=.05 level.

Path c': Subsample Findings

Correlations conducted within the subsample between FA and MD values along both manually defined and atlas-defined white matter tracts and socialization skill were not significant. A similar relationship to the larger group was observed such that the ASD group

showed a negative correlation between FA along both atlas and hand-drawn tracts and socialization skill. Effect sizes for all relationships were smaller for both TD and ASD groups.

Path a: Relationship between FA and Facial Emotion Perception

The correlation between the manually-defined amygdalo-fusiform tract FA and facial emotion perception was not significant within groups or within the overall sample. A scatterplot of this relationship is illustrated by Figure 7. The relationship between tract FA and facial emotion perception contrasts between groups, suggesting a possible interaction. As tract FA increases in TD participants, facial emotion perception increases (the expected direction). As tract FA increases in participants diagnosed with ASDs, facial emotion perception decreases. This is the opposite of the expected relationship.

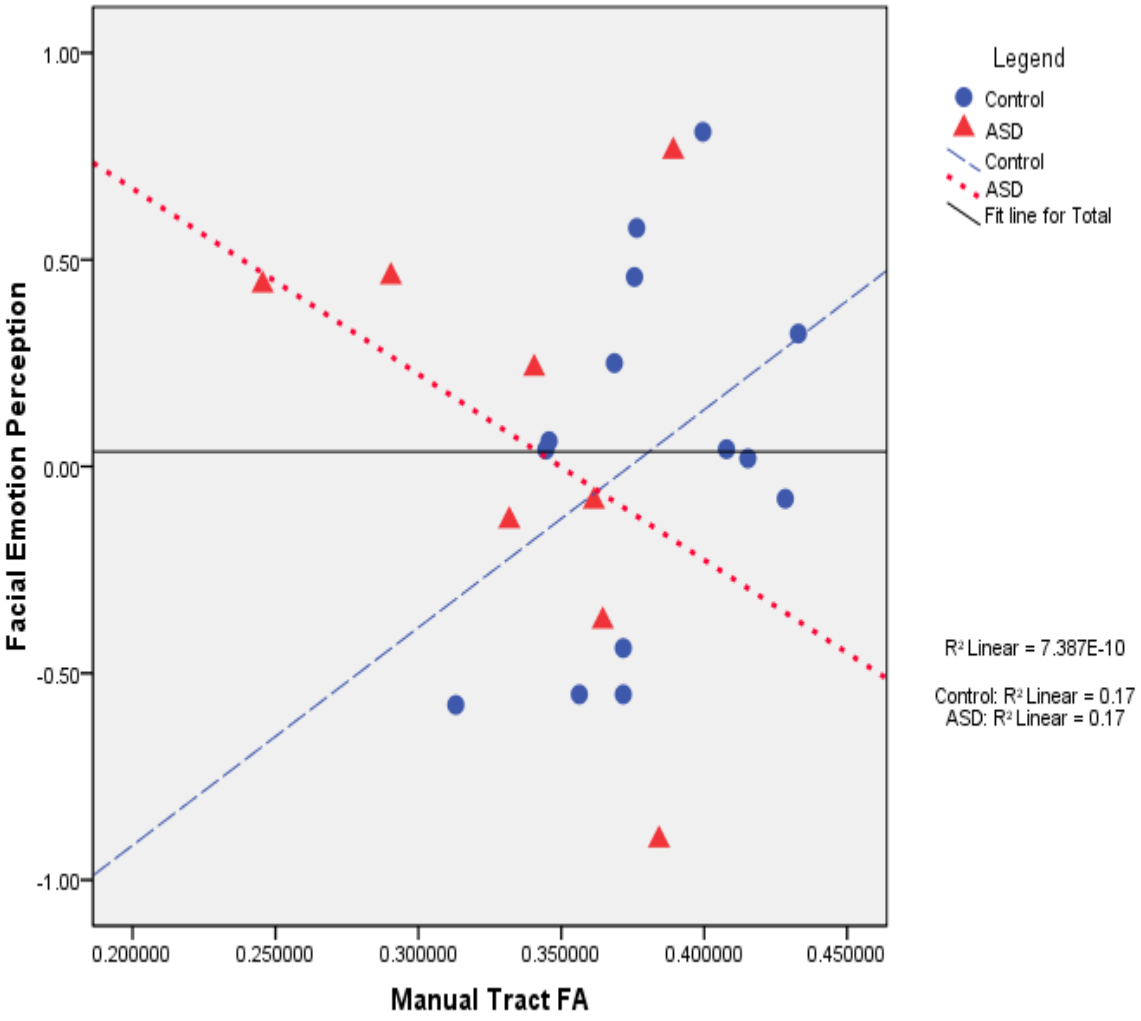

Figure 7. Relationship between manual tract fractional anisotropy and facial emotion perception

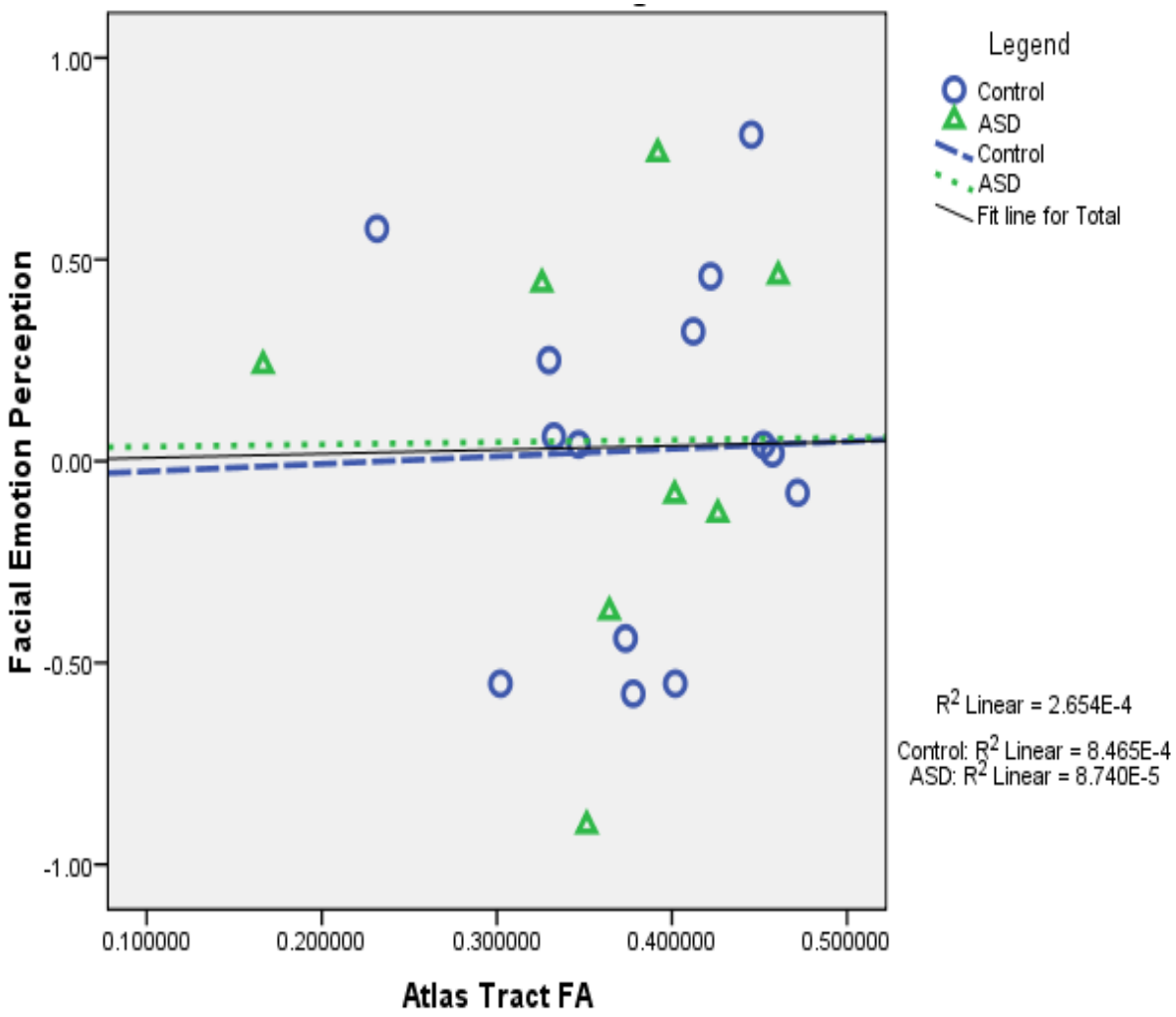

Figure 8. Relationship between atlas tract fractional anisotropy and facial emotion perception

Tract FA explains less than 1% of the variance in facial emotion perception within the mixed group ($R^2 < .001$, p=.99), and 17% of the variance in both TD (R^2=.17, p=.14) and ASD (R^2=.17, p=.31) groups. When the same correlation is presented using atlas-defined tract FA, no relationships are observed with a scatterplot (Figure 8).

No overall or group level significance was determined between mean FA and facial emotion perception. Effect sizes for all relationships showed that FA determined through this method explained less than 1% of the variance in facial motion perception within either group.

Path a: The Relationships between MD and Facial Emotion Perception

A significant correlation was identified in the relationship between tract MD and with facial emotion perception in the ASD group ($r(6)=.70$, $p=.05$). The direction of the relationship was unexpected in that as MD increased, facial emotion perception skill increased (Figure 9). A possible interaction

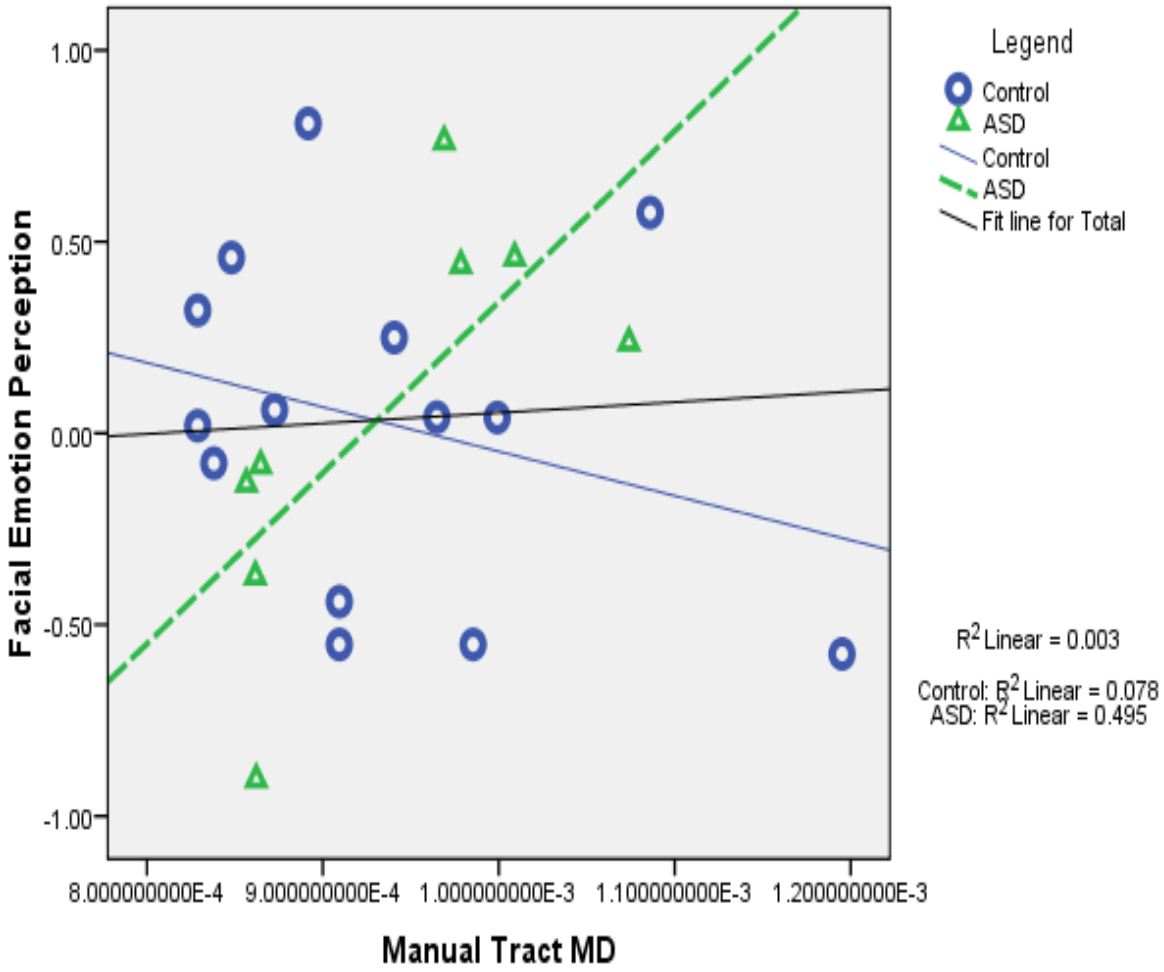

Figure 9. Relationship between manual tract mean diffusivity and facial emotion perception

between TD and ASD groups also was noted in that TD participants demonstrated the expected negative slope. A large effect size was determined such that manual tract MD predicted 50% of

the variance in facial emotion perception in the ASD group (R^2=.50, p=.052). When the same correlation was examined using atlas-defined tract MD, no relationships are observed.

Path a: Subsample Findings

Within the matched sample, no significant relationships between manual and atlas defined tract FA and facial emotion perception could be determined. Similarly, no significant relationships were determined between manual and atlas defined tract MD and facial emotion perception. Effect sizes for all relationships were smaller than the larger sample.

Path b: The Relationship between Facial Emotion Perception and Socialization Skill

Based upon findings in the literature and from a previous study (Hudepohl et al., 2009) that included the majority of participants from the current study, it was hypothesized that a significant positive relationship between facial emotion perception and socialization skill would be replicated within the current sample. A correlation revealed that this relationship was not statistically significant within the mixed sample or within groups. A scatterplot of this relationship is presented in Figure 10. Whereas the control sample's facial emotion perception scores are relatively uniform across socialization skill scores, a positive relationship is noted between these two measures within the ASD group.

As expected, facial emotion perception scores increase along with socialization skill scores. A large effect size was determined such that facial emotion perception score predicted 42% of the variance in socialization skill in the ASD group (R^2=.42, p=.082). No significant difference between group effect sizes was determined per Cohen's (2003) method. Within the subsample, no significant relationships between socialization skill and facial emotion perception could be determined. Effect sizes for all relationships were smaller than the larger sample.

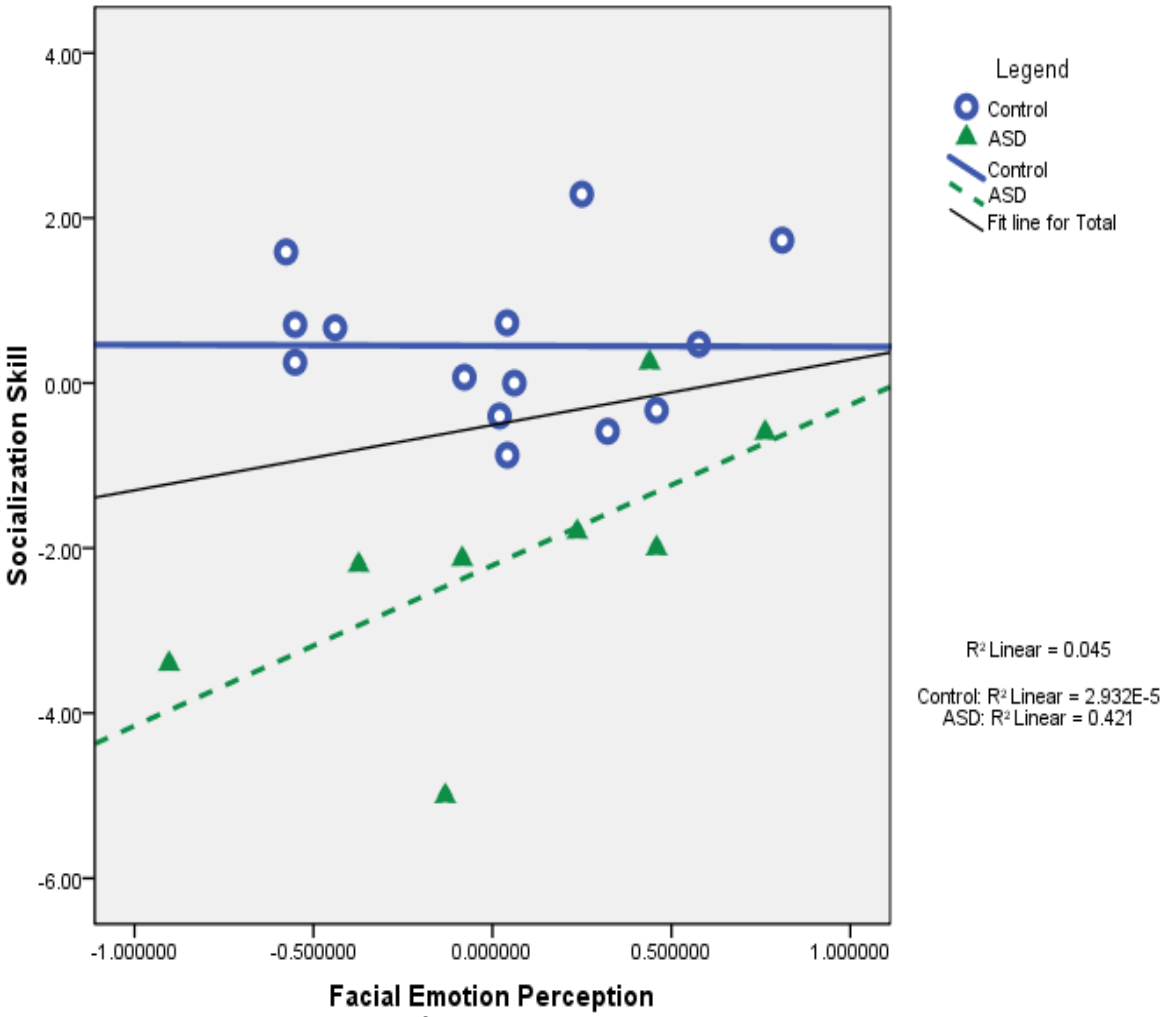

Figure 10. Relationship between facial emotion perception and socialization skill

Relationships between FA and MD along the Control Tract, Socialization Skill, and Facial Emotion Perception

As hypothesized, no significant relationships could be determined between FA values determined along the chosen control tract (right corticospinal tract) and socialization skill within the TD ($r(12) = -.37$, $p = .19$) or ASD ($r(6) = -.11$, $p = .80$) groups. Similarly, no significant relationships were determined between MD values along the control tract and socialization skill in TD ($r(12) = .12$, $p = .68$) or ASD ($r(6) = --.05$, $p = .91$) groups.

No significant relationships were determined between control tract FA and facial emotion perception within TD ($r(12) = .15$, $p = .62$) or ASD ($r(6) = -.20$, $p = .63$) participants. Also, no significant relationships were determined between control tract MD and facial emotion perception within the TD ($r(12) = .22$, $p = .45$) or ASD ($r(6) = .39$, $p = .34$) group.

Aim 3: Mediation Analyses

To address the Aim 3 of this study; a meditational model with facial emotion perception serving as a mediator between white matter integrity and socialization skill (Figure 1) was hypothesized. Baron and Kenney's suggested procedure for testing mediation (Baron & Kenny, 1986) was the selected approach. Significant relationships were expected between all three pathways between variables in the model (a, b, and c in Figure 1). In order to assess the total effect of white matter integrity, this variable would have entered into the first step of a hierarchical regression equation predicting its direct effect on socialization skill (c). To assess the unique effects of each variable in the model, emotion perception would have been entered into the second step of the hierarchical regression along with white matter quality values.

If the predictive influence of facial emotion perception skill was accounted for, it was expected that the strength relationship between mean FA value and VABS-II score would decrease (path c'). If this relationship was rendered nonsignificant, this model would have been considered evidence of a full mediation. This would have meant that emotion perception was the mechanism through which white matter integrity predicted variance in socialization skill for this sample.

As statistically significant relationships could not be established between any of the variables identified in the proposed mediation model identified in Figure 1 for either the full or

matched samples, testing of the mediation was discontinued per the recommendations described by Baron & Kenny (1986).

Exploratory Analyses

In order to increase the sample size available for analyses, a sample that was not limited by the inclusion criteria requiring participants to have completed both facial emotion perception and socialization skill measures was analyzed. This allowed for pairwise comparisons between MD, FA, facial emotion perception, and socialization skill with additional participants that were not eligible for inclusion in the full sample. Descriptive statistics (Table 5.) and group differences (Table 6.) demonstrate that this sample was very similar to the full sample.

Despite similarities, important relationships determined in the full sample were uniquely supported by a significant correlation between FA and facial emotion perception in this sample (Figure 11.). There was a strong positive correlation between manual tract FA and facial emotion perception in the TD group ($r(15)=.54$, $p=.02$). Tract FA explained 30% of the variance in facial emotion perception for the TD group. No significant relationship between manual tract FA and facial emotion perception was determined in the ASD group ($R^2=.10$, $p=.41$), in which manual tract FA explained 10% of the variance in facial emotion perception.

Table 5. Descriptive Statistics for Pairwise Comparison Sample

	ASD (n=9)	TD (n=17)	Group Difference
Age Mean Years (SD) **Age Range**	17.22 (6.93) 11-31	15.75 (5.72) 9-30	NS
% Female	42	54	NS
Ethnicity Count (Caucasian/ Non-Caucasian)	8/1	11/6	NS
WASI FSIQ (SD) **WASI FSIQ Range**	105.88 (17.92) 83-129	108.43 (17.92) 78-128	NS

Note: WASI FSIQ =Wechsler Abbreviated Scale of Intelligence Full Scale IQ; NS= Not Significant

Table 6. Group Differences for Pairwise Comparison Sample

	ASD Group Mean (SD)	TD Group Mean (SD)	p	Effect Size	% Impaired* (ASD,TD)
Socialization Skill[#]	-2.11(1.60)	0.45(0.92)	<.001	d=1.96	75%,0%
Facial Emotion Perception	-.09(0.65)	0.05(0.47)	NS	d=0.25	0%,0%
Manual Tract FA	0.34(.05)	0.38(0.04)	.033	d=0.97	
Atlas Tract FA	0.38(0.04)	0.39(0.05)	.NS	d=0.22	
Manual Tract MD	0.09(0.07)	0.09(0.01)	NS	d=0.01	
Atlas Tract MD	0.09(.01)	0.09(0.01)	NS	d=0.10	
Control Tract FA	0.52(.07)	0.54(.06)	NS	d=0.31	
Control Tract MD	0.09(.01)	0.08(.01)	NS	d=0.02	

Note: [#]=Socialization Skill n(ASD)=8, n(TD)=14; df for all comparisons except Socialization Skill=24; df for Socialization Skill=20; NS=Not Significant; FSIQ=WASI Full Scale IQ; Socialization Skill=Vineland-2 Socialization domain z-score; Facial Emotion Perception=z-score created from absolute value of mean DANVA-II Adult Faces and Child Faces scores; FA=fractional anisotropy; MD=mean diffusivity (all scores x100); *=impaired defined as z-scores of -1.5 or lower

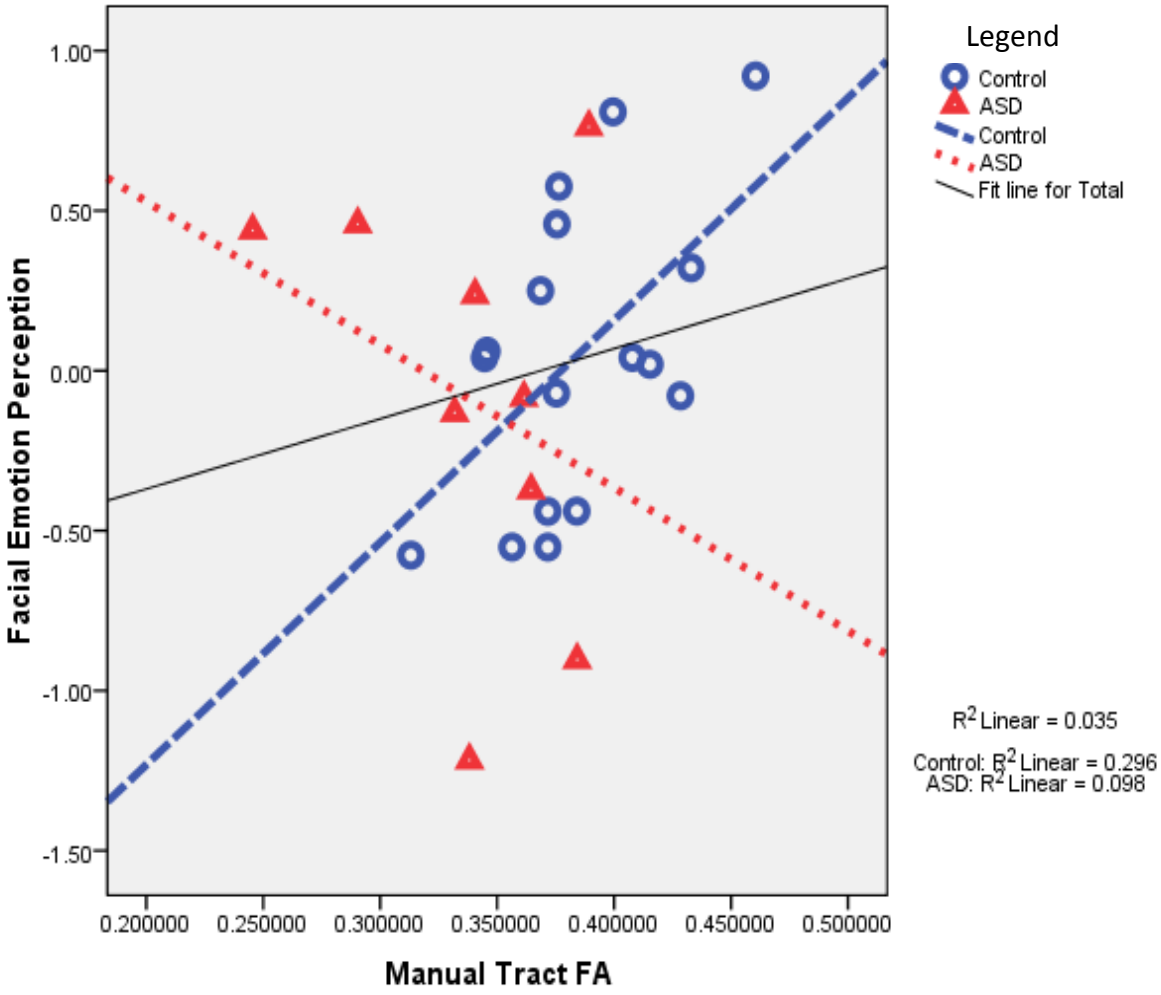

Figure 11. Relationship between manual tract fractional anisotropy and facial emotion perception in pairwise comparison sample.

Figure 12 illustrates the significant positive correlation between atlas tract MD and socialization skill in the ASD group ($r(6)=.80$, $p=.02$). Tract MD explained 65% of the variance in socialization skill for the ASD group. No significant relationship between atlas tract MD and socialization skill was determined in the TD group ($R^2=.10$, $p=.41$), in which manual tract MD explained less than 1% of the variance in facial emotion perception.

Consistent with findings from the original sample described above, no significant relationships could be determined between FA and MD along the control tract and socialization skill or facial emotion perception in either TD or ASD participants in the pairwise sample.

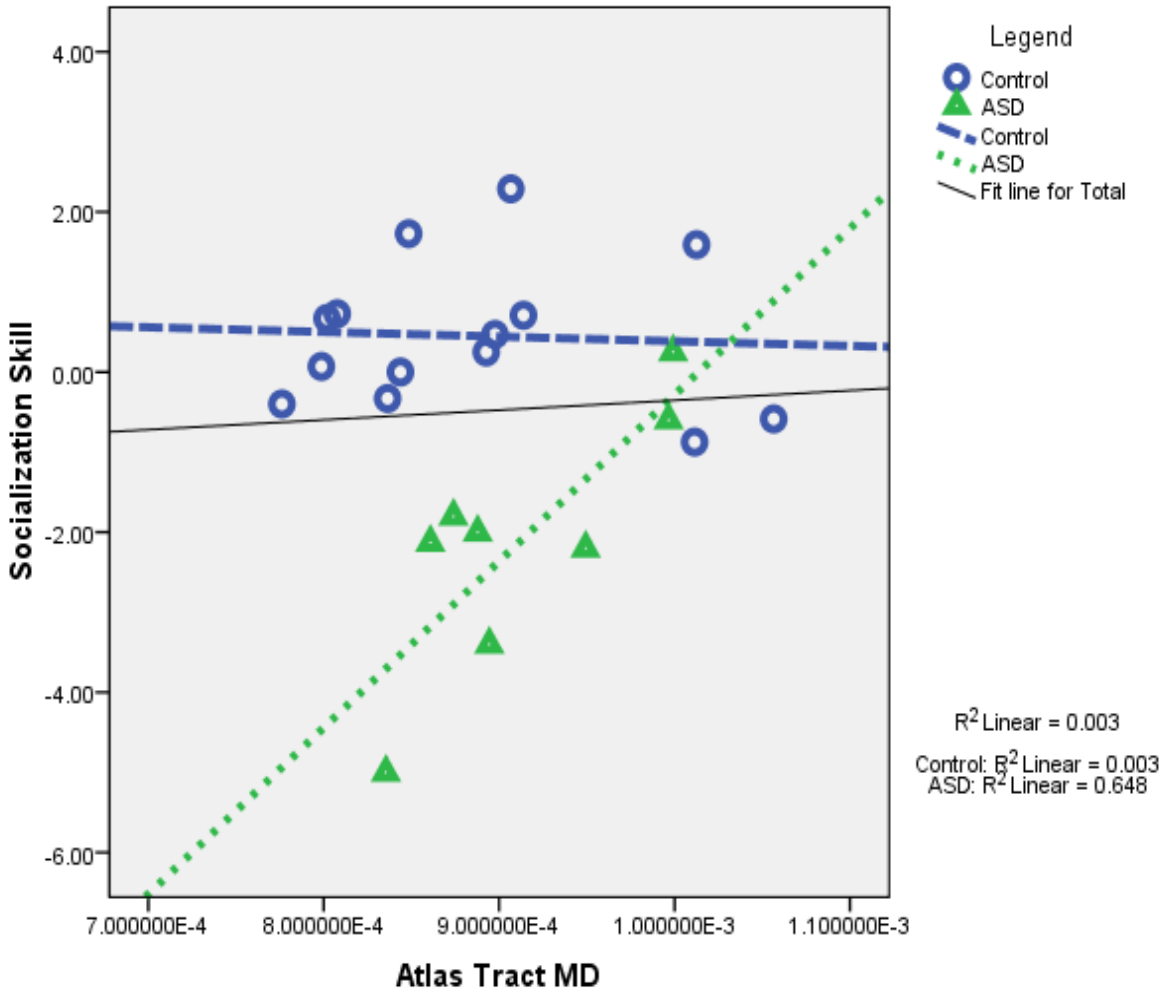

Figure 12. Relationship between atlas tract mean diffusivity and socialization skill in pairwise comparison sample.

Figure 13 summarizes the group differences, strongest relationships, and largest effect sizes between FA, MD, socialization skill, and facial emotion perception for both TD and ASD groups across all of the samples used in the current study.

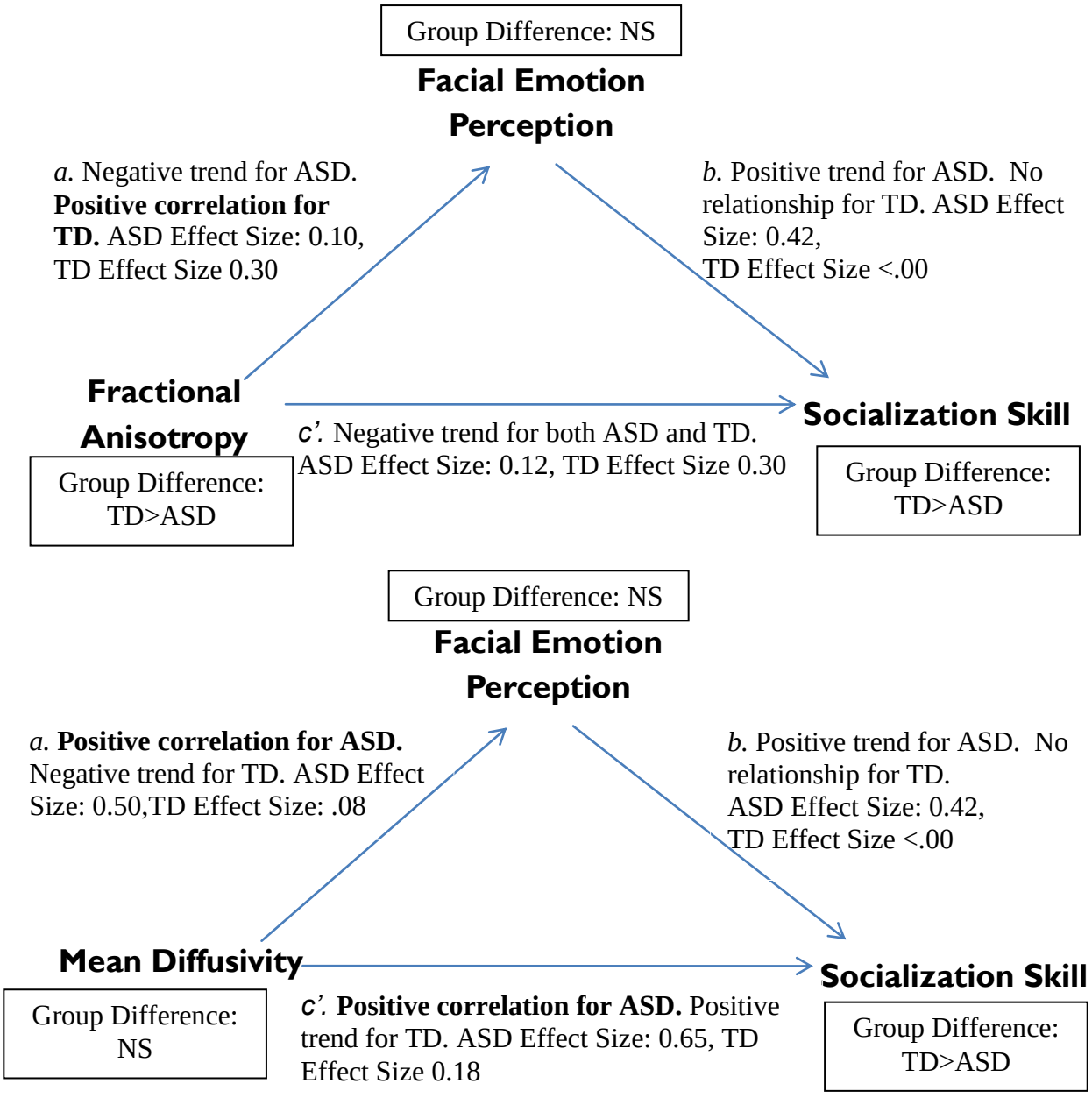

Figure 13. Summarized findings along model paths for fractional anisotropy and mean diffusivity

DISCUSSION

The purpose of the present study was to examine relationships between white matter integrity along the amygdalo-fusiform pathway, facial emotion perception, and socialization skill in a sample of TD participants and participants with ASDs. Diffusion tensor imaging was employed to determine measures of white matter integrity along the amygdalo-fusiform pathway. The study aimed to establish group differences based on white matter integrity between TD participants and participants with ASDs. Aims also included an exploration of the relationship between measures of white matter integrity, facial emotion perception, and socialization skill. Finally, the study was intended to test a mediation model where facial emotion perception was proposed to mediate the relationship between white matter integrity of the amygdalo-fusiform pathway and the outcome measure of socialization skill. As detailed in the results section, the present study included several different approaches to the exploration of the current hypotheses. The discussion below summarizes salient findings across all samples and analyses.

Group Differences based on White Matter Quality, Facial Emotion Perception, and Socialization Skill.

It was predicted that a group-level difference between TD participants and participants with ASDs would be established based on mean FA value measured along the amygdalo-fusiform tract. This hypothesis was supported by findings from the current study. The ASD group demonstrated a lower mean FA than the TD group with a strong effect size. A group difference could not be determined between FA values along the control tract, suggesting that the FA group difference determined along the amygdalo-fusiform tract were specific to this region.

This finding was hypothesized to be evidence of poor white matter quality for participants with ASDs. Lower FA scores in ASD participants support the idea of poorer

structural organization that would have been expected to result in poorer functioning on social behavioral tasks. However, results from the second aim of this study suggest that this interpretation could be inaccurate. Within the ASD group, relationships suggest that increases in FA were related to decreased facial emotion perception and socialization performance. The current study findings of a group difference on tract FA suggests a significant difference in how white matter tracts between two structures important in social function are organized within participants with ASDs vs. controls. Although this finding is important, it also highlights that mean FA in the amygdalo-fusiform tract alone does not provide enough information to assist with our understanding of how differences in structural connectivity result in poorer facial emotion perception and socialization skill.

As expected based upon the relationships presented in the current study and previous literature (Horsfield & Jones, 2002), FA and MD were significantly correlated such that as FA increased, MD decreased with both manually-defined and atlas-defined approaches. Despite this, no significant group differences on MD could be determined. The majority of previous studies have demonstrated increased MD in participants with ASDs compared to controls (Travers et al., 2012). However, the current finding of a significant group difference on FA found in the absence of a significant group difference on MD has been found previously in a sample of participants with ASDs (Catani et al., 2008).

Catani et al. suggest that the degree of uncertainty between measures obtained during tractography and underlying biologic factors makes drawing direct conclusions from FA and MD difficult. The authors also reference earlier studies with neurotypical controls demonstrating uniform MD measures across brain tissues independent of FA differences in specific regions. They suggest that a similar dissociation between FA and MD could be present participants with

ASDs. When taken together with results from the present study, it is likely that FA and MD measures should be interpreted independently as they each contribute unique information about brain tissues, especially in participants with ASDs.

This also suggests that more information is necessary to better define the areas where FA and MD do not overlap. Previous literature suggests that additional microstructural measures that contribute to both FA and MD (including axial and radial diffusivity) should be considered when interpreting group level differences (Budde et al., 2008; Cheng et al., 2010; Nagesh et al., 2008). This is described to be necessary in better defining how both measures reflect specific differences in diffusion caused by changes in myelination theorized to contribute to neurodevelopmental disorders including ASDs.

The ASD group demonstrated significantly lower socialization skill scores than the TD group. Difficulties in this area are common for participants with ASDs. The current ASD sample featured a large percentage (75%) of participants who were impaired on this measure. Based on findings from previous studies described above, this was expected.

The fact that no group difference could be determined on facial emotion perception was unexpected as this area also has been hypothesized as a deficit for many individuals affected by ASDs. A closer examination of the DANVA-2 child and adult facial expressions scores reveals a limited range of responses (all within normal limits) for both ASD and TD groups. It is likely that this measure was not significantly more difficult for participants in the ASD group than for participants in the TD group.

Relationships between White Matter Integrity, Facial Emotion Perception, and Socialization Skill

It was predicted that significant positive correlations would be established between FA along the amygdalo-fusiform tract, facial emotion perception, and socialization skill for both groups. Negative relationships where expected between MD along the target tract, facial emotion perception, and socialization skill. While some significant relationships and trends were determined in the expected directions, data also reflected unexpected relationships, especially within the ASD group. Although all specific hypotheses were not supported, several interesting relationships were observed through careful analysis of effect sizes and data distribution.

White Matter Integrity and Socialization Skill

Trends between tract FA and socialization skill were consistently negative with low effect sizes for participants with ASDs. A medium effect size was determined for the relationship between increases in tract FA and decreases in socialization skill for the TD group. In both cases, the directions of these findings were the reverse of those hypothesized, in that reduced white matter integrity was associated with increased performance on behavioral measures.

As detailed above, increases in FA are often suggested as markers of increased white matter integrity. Increases in white matter integrity are implied to relate to improved functioning. However, a previous study also has found a relationship between increased FA and social impairment in participants with ASDs (Noriuchi et al., 2010). In this study, increased FA in the left dorsolateral prefrontal cortex (DLPFC) was correlated with decreased performance on the Social Responsiveness Scale (SRS). Noriuchi et al. discuss this relationship as evidence of increased structural alteration relating to increased social impairment. When it is considered that

the ASD sample in their study consisted mainly of adolescents, and higher FA values were found in a prefrontal region, it is possible that the increased FA values are evidence of an altered white matter developmental path beginning with early over-myelination for participants with ASDs. This over-myelination may relate to over-connectivity between social brain structures and poorer performance on social tasks (Cheng et al., 2010; Weinstein et al., 2011) and is a topic that will be revisited later in this discussion. However, this explanation does not entirely explain findings in the current study when the wide age range of the present sample and the finding of lower mean FA along the amygdalo-fusiform tract for the ASD group vs. the TD group are considered.

Measures of FA and MD are related such that both are determined through measurement of diffusion along three principal directions of water diffusion in tissue. Where FA involves a manipulation of this information to include overall directional flow, MD is simply an average of diffusion across all directions. Both measures rely upon the same information. Therefore, it is not surprising that the association between tract MD and socialization skill was also in the opposite direction for both groups than that which would be expected based on previous literature.

Increases in MD along white matter tracts, commonly suggested as an indication of poor white matter quality (Nagae et al., 2012; Sundaram et al., 2008), were accompanied by increases in socialization skill in both TD and ASD groups. A significant positive correlation between MD and socialization skill was determined in the ASD group, whereas a positive trend between these variables in the TD group. These current and past findings of positive correlations between MD and social skills conflict with results from a recent review of DTI studies with ASD samples that suggests an overall trend of increased MD and poorer social functioning in participants with ASDs (Travers et al., 2012)

Participants with ASDs in this sample demonstrated poorer scores on socialization skill than TD participants. Socialization is a set of a complex behaviors likely influenced by factors beyond facial emotion perception. As such, it is likely that a larger network of white matter connectivity could better explain why the current results did not support hypothesized findings. Connections between the superior temporal sulcus and amygdala, and white matter tracts between the amygdala and frontal cortical systems have been hypothesized as contributing factors in social deficits in the ASD spectrum (Ke et al., 2009; Sundaram et al., 2008). It is possible that examining a single tract is inadequate in providing an understanding of the complex systems involved in socialization skill. Future studies should consider the exploration of an expanded white matter network in the study of socialization skill.

White Matter Integrity and Facial Emotion Perception

In contrast with the hypothesized relationship, the current study data suggest an association between increased FA and decreased performance on a measure of facial emotion perception for participants diagnosed with ASDs. The TD group demonstrated a positive correlation between FA and facial emotion perception, supporting the current hypothesis. In the ASD group, a positive correlation demonstrated that increased MD was related to increased facial emotion perception. This finding contrasts with hypothesized expectations and previous research (Welchew et al., 2005; Wicker et al., 2008). Although the relationship between increased MD and poorer facial emotion perception was not significant in the TD group, the distribution of these variables suggests the hypothesized relationship, and is consistent with the previous literature.

Correlations between white matter integrity and behavioral measures did not consistently suggest relationships similar to the majority of the previous literature, and did not uniformly

support the current hypotheses. However, it is clear that our current understanding of the relationships between measures of white matter integrity and the specific biological differences they aim to describe requires further development. This improved understanding is necessary before FA and MD can be applied as absolute indications of better or worse white matter integrity, especially if associations between white matter integrity and measures of behaviors as complex as social functioning are to be made.

There has been considerable variability in FA and MD findings in previous studies with ASD samples. Findings from the current study suggest a group level difference in how white matter quality should be conceptualized in participants with ASDs. This is consistent with a subset of studies discussed above suggesting that relationships between white matter integrity and social impairments in ASD samples may need to be conceptualized differently to how these relationships are interpreted in typical samples.

Support for a difference in the conceptualization of white matter quality in ASDs has roots in our understanding of how the brain develops in this population. It has been suggested that white matter development for individuals affected by ASDs follows a path that is markedly different than their typically developing peers (Courchesne et al., 2001). Over-growth within the first year of development has been identified in multiple brain tissues by previous literature (Courchesne et al., 2003). This abnormal period of growth has been hypothesized to be the result of impaired neuronal pruning (Frith, 2003), and is quickly followed by a period of decelerated neural development (Dawson et al., 2007).

Specifically of interest to the current findings, the amygdala in groups with ASDs demonstrates more growth than controls during childhood, but is underdeveloped when compared to TD groups when measured at adolescence (Schumann et al., 2004). Frontal areas of

the cortex are especially affected by early white matter overgrowth (Ben-Bashat et al., 2007), and relationships between indications of over-myelination in these areas has been related to poor performance on emotion processing measures (Wicker et al., 2008). As FA is particularly sensitive to myelination, it is possible that higher FA values in participants with ASDs are capturing over-myelination and not increased white matter integrity as would be expected in a typical sample. Thus, higher FA values may not be expected to relate to higher functioning across clinical and control samples.

The role of age should be considered in any study examining neuroanatomical correlates in ASDs. While covarying for age did not make the relationships between measures of white matter integrity and social behavioral measures statistically significant, it should be noted that the current study featured a sample of participants with a wide age range spanning a period in development when a considerable reorganization of white matter tissue has been hypothesized (Cheng et al., 2010). Within the ASD sample, differences in white matter development may account for neuroanatomical dissimilarities that contributed to a possible group interaction on the relationships between white matter integrity and facial emotion perception.

When relationships between measures of white matter integrity and social behavioral measures were explored in the current study, effect sizes for MD measurements were consistently higher than those for FA. This suggests that MD (possibly as a result of being a more direct, less mathematically adjusted measure of diffusion compared to FA) offers additional information beyond what FA provides, especially within ASD samples. This suggests that future research is warranted to examine the relationships between MD and social behavior variables with a larger sample of individuals with ASD.

Whereas previous articles suggest considerable variability between measures of FA and MD within participants with ASDs, there was strong evidence that a positive relationship would have been detected between facial emotion perception and socialization skill, especially given findings from a previous study with overlapping participants from the current sample (Hudepohl et al., 2009). Though this relationship was not found to be significant, a positive trend was identified between these measures in the ASD group. No relationship could be identified for TD participants.

The restricted range of facial emotion perception scores for TD participants is likely to have played a large role in this. Also, whereas previous work with the DANVA2 has employed the use of the entire measure, or a single facial emotion subscale as in Ingersoll et al. (2010) , this is the first study that the author is aware of to use only a combined facial emotion scale. However, when relationships between FA, MD, socialization skill and the entire DANVA2 where explored, no significant relationships where observed.

Exploratory Analyses

Parallel analyses to those described above were conducted with FA and MD values calculated within the fusiform face area and amygdala independently for TD and ASD groups. No significant relationships were determined, effect sizes were generally in the small to medium range, and lower than tract-level analyses across groups overall. These findings suggest support for previous literature calling for neuroimaging studies to apply a multi-structure connectivity-based approach in place of individual ROI analyses in understanding relationships between brain structures and behavior (Fein, 2011; Verhoeven et al., 2010).

In order to explore the relationships between variables in the proposed model (Figure 1) where ADOS Social Interaction Total (ADOS-SIT) scores replaced facial emotion perception

scores as a potential mediator, correlations between ADOS-SIT scores, white matter quality measures and socialization skill as measured by the VABS-2 were conducted within the ASD group. No significant relationships could be determined between ADOS-SIT scores and any white matter measure or ADOS-SIT scores and socialization skill in the model. Effect sizes for ADOS-SIT scores in these relationships were comparable to the associations between facial emotion perception and the other variables.

As no significant relationships between variables could be determined, the alternate mediation model with ADOS-SIT scores could not be tested. There was a negative trend between ADOS social interaction scores and socialization skill scores. ADOS social interaction scores were not found to be related to white matter measures as had been determined by previous literature (Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2007). While there was a considerable range in ADOS scores within this sample, the effect of the relatively small sample size of participants with ASD's is likely to have contributed to these null findings.

Atlas-Defined White Matter ROIs vs. Manually Defined White Matter ROIs

Findings from the present study allow a comparison between an amygdalo-fusiform tract defined by ROIs created manually and the tract created between atlas-defined ROIs. Overall, no significant differences between groups or unique relationships among variables were found using the atlas-based method. Effect sizes from correlation analyses were generally larger for the manual approach versus atlas-based approach. Mean tract FA values determined through manual and atlas-defined approaches were not significantly related. Similarly, mean tract MD values determined through manual and atlas-based MD approaches were not related. This is likely due to many factors.

Manually-defined ROIs allow experimenters to carefully delineate boundaries along grey and white matter boundaries. This is especially important in probabilistic tractography as a failure to include white matter in each structure that is likely to include part of estimated tract can result in inaccurate tract estimations (Jones, 2008). Previous studies have demonstrated larger effect sizes (Hagler et al., 2009) with atlas-based approaches compared to manually defined ROIs. However, this comparison has not been tested with ROI seed points that include both grey and white matter. This is especially important when it is considered that the amygdala ROI used in the current study was composed of a considerable portion of grey matter. Subcortical brain atlases are not optimized for diffusion tensor imaging and often do not take the white matter adjacent to structures canonically defined as grey matter into account. This is a difficulty that can be alleviated by a manual-selection approach.

The fusiform face area utilized in the atlas-defined approach also was limited by a non-specific ROI composed of a sphere centered on an average region of activation. In many cases, the sphere included a considerable area of grey matter. This method also introduced the possibility of including portions of large white matter tracts leading to regions adjacent to (but separate from) the fusiform gyrus. Inclusion of these tracts would make it more difficult for a tractography algorithm to accurately estimate white matter tract position. This is due to the weakness of probabilistic tractography in estimating the correct path direction in areas with large numbers of fibers crossing over a small area (Jones, 2008).

An additional concern in using atlas-based ROIs is that standardized brain atlases are formed using a given normative sample with a limited amount of brain tissue differences. This suggests that despite the improved standardization (and related reliability) atlas-based approaches provide; the flexibility that manual approaches allow for is better able to account for

individual white matter differences between subjects. This is especially true for clinical and pediatric samples as normative samples used to create brain atlases are usually composed of adult typically developing participants. This is an important consideration for the present study as the sample in the present study included younger participants in both the clinical and typical groups. Based upon these findings, the discussion above was based on results determined with the manually-defined method.

Limitations

There are several important limitations to this study that must be considered when findings are discussed. The limitation that is likely to have the strongest potential influence on results is the relatively small sample size (especially within the ASD group). The small sample in the current study suggests that findings are less stable and therefore less reliable. This also may account for some of the variability in findings discussed above. Results from power analyses conducted before the study findings suggested that analyses using the small sample size would be underpowered. Based upon results presented above, this appears to have been confirmed. Individual analyses effect sizes suggested that the relationship between tract MD and socialization skill would have been significantly related in the ASD sample (though an unexpected direction) with a larger sample size. The relationship between tract MD and facial emotion perception may have been significantly related in the ASD sample given a larger ASD sample, such that increases in MD would have been related to better facial emotion perception. Of note, two previous studies were able to find significant correlations between white matter variables and behavioral measures with a similarly small sample size (Barnea-Goraly et al., 2004; Noriuchi et al., 2010)

A similar trend suggested that a larger sample size would have allowed previously established findings of a significant relationship between facial emotion perception and socialization skill to be replicated in the current study. This would have allowed for an MD-based mediation model to be tested describing a relationship between the three factors suggested by the original hypothesis with an ASD sample. The current sample also included predominantly high functioning individuals with ASDs. As the ASD phenotype covers a broad spectrum of individuals, additional variance presented by a wider sample of participants along the spectrum may have allowed for a more representative simulation of deficits present in the ASD population.

The use of facial emotion perception measures from the DANVA-2 presented an additional limitation. The DANVA-2 featured static images as stimuli. Static images allow for the measurement of facial emotion perception with fewer factors (e.g. motion and sound) to recruit input from areas of the brain outside the fusiform face area. Unfortunately, this type of stimuli is not an ecologically valid representation of the day-to-day dynamic facial emotion perception tasks participants with social deficits would find more difficult. This lack of difficulty also is likely to have contributed to the restricted range of scores on this measure (all TD and ASD scores within normal limits).

The brain-behavior relationship component of the study suffered a major limitation in the approach used to define ROI boundaries for the fusiform face area. As reliable anatomically defined boundaries have yet to be defined for the fusiform face area, the ideal approach to the creation of an FFA ROI on a structural image is accomplished through the guidance of an FFA localization task (Pierce et al., 2001). This is because the FFA region on the fusiform gyrus is in a slightly different location for most participants, and may be especially difficult to find in

participants with ASDs (Grelotti, Gauthier, & Schultz, 2002). The current study did not include an FFA activation task that could be used to assist with the establishment of ROI boundaries. As a result, it is likely that some of the white matter pathways included in the target ROIs were fibers travelling to other areas of the fusiform gyrus and not direct connections to fusiform face area. A study able to apply the combination of functionally-defined FFA ROI and a structurally-defined amygdala may be more successful in investigating the amygdalo-fusiform pathway.

An additional approach to improving the accuracy of both FFA and amygdala boundaries in this study would have been standardizing individual structural and diffusion volumes using standardized templates better tailored to each participant's age and brain size (Wilke, Holland, Altaye, & Gaser, 2008). Our current approach of using a single standardized brain space (MNI) for each participant means that each individual's data was forced into the standard template regardless of age or brain size. The use of individual templates standardized by age would allow a comparison between individual data (especially for younger participants) without sacrificing the accuracy usually lost by using a single standard space for all participants.

Finally, as discussed in previous literature, the white matter pathway between the amygdala and fusiform gyrus is not defined by anatomical boundaries. Therefore, the pathways were created through probabilistic tractography for TD and ASD groups could not be verified with anatomical reference points. Despite this, pathways similar to those found by Conturo (2008) and Smith (2009) were determined for both ASD and TD groups. There are also limitations presented by the use of probabilistic tractography to estimate this path, as this relatively new approach is continually developing and particularly sensitive to noise presented by white matter tracts crossing perpendicular to the target path (Jones, 2008).

Study Strengths

The current study featured a sample of participants who underwent rigorous behavioral training paradigm to assist with high-quality image acquisition. Data also was processed with statistical motion correction software. As a result, few participants were excluded based on motion artifact. Given the sensitivity of DTI data to motion, this suggests the advantages of including these precautions in future DTI studies. Continued efforts to improve these methods increase the likelihood that future studies will be able to include additional participants on the Autism spectrum with a higher level of impairment.

An additional strength of the current study is the use of theory driven hypotheses. Tract selection was guided by the hypothesis of an amygdalo-fusiform pathway related to social cognition as suggested by Schultz (2005). The majority of previous DTI studies employ whole brain exploratory analyses (i.e. Tract-Based Spatial Statistics) to determine group level differences in white matter integrity. Few studies are guided by previously determined theories suggesting the exploration of specific white matter tracts. The current study also featured a control region to test the specificity of white matter differences along the target tract. Often, differences in white matter quality are first determined through these exploratory methods and then links between differences in areas throughout the brain and behavioral symptoms are suggested. Theory-based approaches will allow the field to test and expand upon previously determined theories within neuroimaging and build upon findings from established literature outside of neuroimaging with more precision.

The current study provides both significant correlations and nonsignficant trends suggesting associations between measures of white matter integrity and indices of social functioning in participants with ASDs. Effect sizes determined in the current study will be

helpful in identifying relationships likely to be significant with a larger sample or with an improved tractography approach in future studies. The finding of a possible group-level interaction between mean diffusivity and facial emotion perception builds upon body of literature suggesting relationships between specific neurological structures and specific behavioral measures in participants with ASDs. This underscores the importance of continuing research into group differences between structural connectivity and behavioral measures.

Few studies have allowed for a comparison of multiple white matter tractography methods within the same group of participants. As there is no current "gold standard" approach to white matter tractography, continued exploration of the most effective methods in studying both TD and clinical populations will be useful until a field standard is determined.

Future Directions

Future research continuing the study of white matter integrity along the amygdalo-fusiform pathway may consider extending the investigation to the left hemisphere. The current study restricted analyses to the right side amygdala and fusiform gyrus as the majority of previous findings were reported there, but important differences between ASD and TD groups have also been found in the left hemisphere in previous studies (Ke et al., 2009; Noriuchi et al. 2010; Conturo et al., 2008).

In addition to measures of FA and MD, future studies should obtain additional diffusion data including AD and RD to assist with the interpretation of results. While FA and MD are commonly cited as measures of white matter quality, microstructural differences indicated by individual diffusion components can also be important factors (Budde et al., 2008; Nagesh et al., 2008). Studies including these microstructural indices of white matter integrity will be able to better explain more specific factors that result in changes in FA and MD (Lee et al., 2007).

Further investigation along this vein will assist in determining what contributed to MD emerging as a stronger indicator than FA for the ASD group in the present study.

Finally, a helpful extension of the present study could be a mediation model exploring relationships between white matter quality along tracts in an expanded social brain network including the superior temporal sulcus and dorsolateral prefrontal cortex. Future studies may consider the study of tracts between the amygdala and frontal regions, tracts between the amygdala and superior temporal sulcus, and tracts between frontal regions and the superior temporal sulcus. As facial emotion perception and socialization are complex behaviors, the extension of the current theory to a larger model driven by previous studies suggesting connections between these additional areas would provide a greater understanding of the underlying factors behind the white matter and social deficits present in participants with ASDs.

In summary, the primary results from the present study supported previous findings of a mean deficit in FA along a specific white matter pathway for participants with ASDs, and replicated a less common finding of no group difference on MD. A positive relationship between FA and facial emotion perception was determined in the TD group, supporting the current hypothesis. Within the ASD group, a positive correlation between MD and facial emotion perception and a positive correlation MD and socialization skill contrasted with the negative relationships that were hypothesized between these measures. The data distribution and considerable effect sizes suggested negative relationships between FA and socialization skill for both groups.

A group interaction was illustrated for FA and facial emotion perception such that participants with ASDs demonstrated an unexpected negative trend, while typically developing participants displayed the hypothesized positive relationship. This interaction was further

demonstrated by the positive correlation between MD and facial emotion perception in the ASD group with the TD group demonstrating a negative trend. This suggests that measures currently interpreted as indices of greater white matter integrity by studies with typically developing participants, may need to be conceptualized differently in participants with ASDs. A strong effect size accompanied the positive trend between emotion perception and socialization skill in ASD participants. Future studies should continue to employ theory driven hypotheses, utilize larger samples, and consider the range of abilities as well as developmental stage of neural development in both ASD and TD groups.

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