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THE EXAMINATION OF WHITE MATTER MICROSTRUCTURE, AUTISM TRAITS, AND

SOCIAL COGNITIVE ABILITIES IN NEUROTYPICAL ADULTS

by

LAUREN E. BRADSTREET

Under the Direction of Diana L. Robins and Tricia Z. King

ABSTRACT

The purpose of this study was to examine the relationships among mentalizing abilities, self-reported autism traits, and two white matter tracts, uncinate fasciculus (UF) and inferior longitudinal fasciculus (ILF), in neurotypical adults. UF and ILF were hypothesized to connect brain regions implicated in a neuroanatomical model of mentalizing. Data were available for 24 neurotypical adults (mean age = 21.92 (4.72) years; 15 women). Tract-based spatial statistics (TBSS) was used to conduct voxelwise cross-participant comparisons of fractional anisotropy (FA) values in UF and ILF as predicted by mentalizing abilities and self-reported autism traits. Self-reported autism traits were positively related to FA values in left ILF. Results suggest that microstructural differences in left ILF are specifically involved in the expression of subclinical autism traits in neurotypical individuals.

INDEX WORDS: Diffusion tensor imaging, Mentalizing, Theory of mind, Uncinate fasciculus, Inferior longitudinal fasciculus

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SOCIAL COGNITIVE ABILITIES IN NEUROTYPICAL ADULTS

by

LAUREN E. BRADSTREET

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Georgia State University

2014

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December 2014

DEDICATION

This work is dedicated to my sister, Maddie, and my brother, Jack.

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Numerous individuals have encouraged me and stimulated my thinking for this project. First, I would like to thank my mentor, Dr. Diana Robins, for her support and guidance during this project and beyond. I find her unwavering belief in me invaluable. I am also grateful for the support of my committee members, Dr. Tricia King and Dr. Jessica Turner. Their insightful discussions with me made this project a truly invigorating learning experience. Additionally, I am indebted to Dr. Erin Hecht for her patience and generosity of knowledge. Her technical guidance made this project possible.

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Finally, I am incredibly grateful to have love and encouragement from my family, friends, and partner. These individuals enrich my life, and it is their support that makes my pursuit of knowledge possible.

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1   INTRODUCTION

Social cognition is broadly defined as the ways in which human beings think about themselves and the social world, including how they select, interpret, remember, and use social information (Aronson et al., 2010). From this definition, it is clear that social cognition draws upon numerous cognitive skills. Three general sets of cognitive processes build upon and interact with one another to produce complex social behavior (Adolphs, 2003). Perceptual processes allow for the detection of social stimuli in an environment. These representations of social stimuli are then associated with emotional responses, cognitions, and behavioral motivations. Finally, higher cognitive processes produce an internal model of the social environment, including representations of other people, others' relationships to oneself, and the impact of one's actions in a social context (Adolphs, 2003).

Impairments in social cognitive skills are defining features of autism spectrum disorder (ASD) and are present in many other neurodevelopmental and neurodegenerative disorders. Given this, much attention has been directed at understanding the neural substrates of social cognition. The coordinated activity of multiple cortical and subcortical brain regions generates the complex processes involved in social cognitive skills (Adolphs, 2003; Abu-Akel & Shamay-Tsoory, 2011; see Koziol & Budding, 2009). Although a large body of literature examines specific brain structures that are implicated in various forms of social cognition (see Adolphs, 2003 and Blakemore, 2008 for reviews), less attention has been given to examining white matter pathways that connect these regions. The present project contributes to filling this gap by examining the relationships among white matter microstructure, self-reported symptoms of ASD, and social cognitive skills in neurotypical adults. A review of the literature on one aspect of social cognition, mentalizing, is presented first, followed by an overview of the proposed project.

1.1 DEFINITION OF MENTALIZING

Mentalizing, also known as theory of mind, is the ability for humans to make inferences about the thoughts, emotions, desires, and beliefs of themselves and others (Frith & Frith, 2006; Lombardo et al., 2010; Seigal & Varley, 2002). For the purposes of this review, the term "mentalizing" is used and is considered synonymous with the construct "theory of mind." Mentalizing involves an awareness of one's own internal mental state, the recognition that other conspecifics possess their own internal mental states that differ from one's own, and the ability to predict another's mental state and behavior based on direct social cues (e.g., facial expressions, body movement, vocalizations) and contextual factors (e.g., external events, social knowledge). This complex cognitive process begins to emerge around age 18 months and becomes explicit between ages 4-6 years (Frith & Frith, 2003). The ability to "know" the mental states of others is integral to successfully interacting with others and predicting their actions (Frith & Frith, 2006).

"Knowing" another's mental state begins with basic cognitive processing of perceptual cues in different modalities (Frith & Frith, 2006). Much attention has been given to the perception of social behavior from visual cues. Even in the absence of what are intuitively considered "social cues," such as facial expressions, body movements, and gestures, humans are quick to perceive social relationships based on simple types of movement, even between non-living objects (Heider & Simmel, 1944). In a foundational study of social cognition, Heider and Simmel (1944) examined basic movement cues that contributed to the perception of social behavior using a short animated film clip of geometric shapes. The majority of participants readily perceived relationships among the shapes and ascribed intentions, emotions, and personality characteristics to them. The authors concluded that certain types of movement, such

as when objects appear to "follow" one another or "react" to the movement of other objects, induce the perception of social behavior. Subsequent studies using similar stimuli have replicated the finding that neurotypical individuals are quick to perceive and describe social relationships among non-living stimuli based on specific types of perceptual cues (e.g., Blakemore et al., 2003; Castelli, Frith, Happé, & Frith, 2002; Klin, 2000; Klin & Jones, 2006).

Objects that are perceived to be animate agents of action trigger the mentalizing ability of humans. Two features that contribute to the detection of agency are the type of motion, referred to as animacy, and the interaction between objects, known as contingency (Blakemore et al., 2003). Animate motion is perceived as self-propelled or internally directed with "non-Newtonian" changes in velocity. Contingency can be perceived as either mechanical or intentional/social. Mechanical contingency consists of a physical relationship between objects that follows Newtonian laws of motion. A collision of billiard balls demonstrates this type of motion. In contrast, intentional/social contingency consists of causation at a distance. When an object appears to "react" or "respond" to the movement of a distant object, humans perceive that object to be driven by internal goals (Blakemore et al., 2003). Objects that appear to produce animate-contingent motion – that is, self-propelled and responsive motion – are perceived to have agency and "minds" of their own.

Numerous other perceptual cues aside from motion activate the mentalizing ability of humans. More complex cues that help humans "know" the minds of others include facial expressions, gestures, and eye gaze (Adolphs, 2003). Facial expressions are among the most used stimuli in studies of social cognition (e.g., Adolphs, Tranel, & Baron-Cohen, 2002; Kennedy & Adolphs, 2012; Miyata et al., 2010), and are clear signals of internal emotional states. The direction of eye gaze and communicative gestures, such as pointing, are also rich sources of

information for inferring the direction of attention and motivation of others (Langton, Watt, & Bruce, 2000). These cues occur in a particular context, and an individual's knowledge of that context and his or her previously acquired social knowledge contribute to the ability to infer mental states (Frith & Frith, 2006).

The detection of social cues in the environment and in the context of acquired social knowledge lead to two dissociable forms of mentalizing: cognitive mentalizing and affective mentalizing (Brothers & Ring, 1992; Abu-Akel & Shamay-Tsoory, 2011). Cognitive mentalizing primarily involves understanding knowledge, beliefs, and thoughts, whereas affective mentalizing involves understanding emotions and affective intentions (Brothers & Ring, 1992). Additionally, a further distinction is made between mentalizing in regard to the self (i.e., thinking about one's own internal mental states) versus others (i.e., thinking about the mental states of others). A variety of tasks have been developed to measure these forms of mentalizing. Some, such as the Reading the Mind in the Eyes task (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001), assess affective mentalizing by asking individuals to judge the emotions of others based on facial cues. Other tasks focus on cognitive mentalizing by evaluating whether individuals are able to recognize when their beliefs/knowledge differ from those of others (i.e., first-order false beliefs) and to recognize when others may have different beliefs/knowledge from one another (i.e., second-order false beliefs; see Elamin, Pender, Hardiman, & Abrahams, 2012 and Adolphs, 2003 for reviews of commonly used mentalizing tasks).

1.2   NEUROANATOMICAL MODEL OF MENTALIZING

Social cognitive abilities, including mentalizing, arise from neural networks comprised of multiple brain regions (Kennedy & Adolphs, 2012). Numerous functional magnetic resonance imaging (fMRI) studies have investigated brain structures active during tasks that tap into each

type of mentalizing. After a review of the literature, Abu-Akel and Shamay-Tsoory (2011) proposed a neuroanatomical model of mentalizing. This comprehensive model details the interconnected networks of cortical and subcortical brain regions that give rise to both cognitive and affective mentalizing of the self and others. As stated by Abu-Akel and Shamay-Tsoory (2011), the goal of this model is to explain three mentalizing processes: "to represent cognitive and affective mental states, attribute these mental states to self and others, and finally apply (or deploy) these mental states… to correctly understand and predict behavior" (pp. 2971-2972). The focus of this review will be on the neuroanatomical structures that underlie these cognitive processes. A schematic diagram adapted from Abu-Akel and Shamay-Tsoory (2011) that illustrates the neural circuits underpinning this proposed mentalizing system in the brain is shown on the next page (see Figure 1.1). These circuits and their associated brain regions are discussed in the following review.

Distinct neural circuits produce cognitive and affective mental states; however, certain brain structures play a role in both forms of mentalizing and are considered components of both circuits. The temporoparietal junction (TPJ), one of the brain regions consistently implicated in mentalizing tasks (Frith & Frith, 2006), is one such region. Although the TPJ consists of anatomically distinct areas, including the posterior superior temporal sulcus (pSTS) and the inferior parietal lobule (IPL), the combined activations of these regions are hypothesized to be critical for the representations of cognitive and affective mental states (Decety & Lamm, 2007). The superior temporal sulcus (STS), which includes the pSTS and extends to the anterior region of the temporal lobe, and posterior cingulate cortex/precuneus (PCC/PCun) are two additional areas that are components of both neural circuits for cognitive and affective mentalizing.
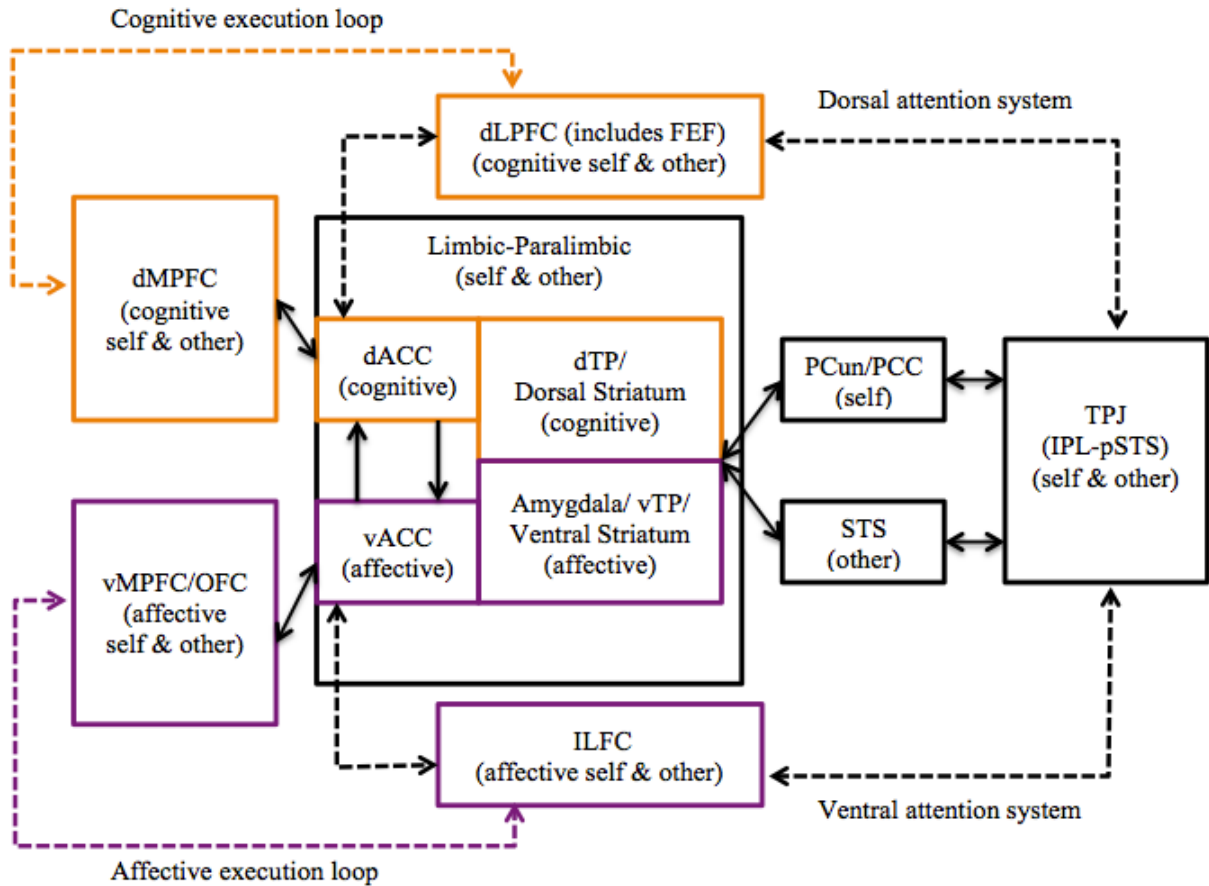
Figure 1.1 Diagram of Neuroanatomical Model

Adapted from Abu-Akel and Shamay-Tsoory (2011). Black boxes = cognitive and affective mentalizing; orange boxes = cognitive mentalizing; purple boxes = affective mentalizing. TPJ = temporoparietal junction; IPL = inferior parietal lobule; (p)STS = (posterior) superior temporal sulcus; PCun = precuneus; PCC = posterior cingulate cortex; (d/v)TP = dorsal/ventral temporal pole; (d/v)ACC = (dorsal/ventral) anterior cingulate cortex; dLPFC = dorsal lateral prefrontal cortex; ILFC = inferior lateral frontal cortex; (d/v)MPFC = (dorsal/ventral) medial prefrontal cortex; OFC = orbitofrontal cortex

Activity in the pSTS, a region that is considered to be within the TPJ in the model by

Abu-Akel and Shamay-Tsoory (2011), is involved in the perception of socially relevant cues in

the environment. Of particular interest is the observation that bilateral pSTS regions respond

differentially to biological motion – motion that is animate and distinctly created by human or

animal bodies, faces, or limbs (Johansson, 1973; Blakemore et al., 2003) – depending on the

context in which the motion is perceived (Materna, Dicke, & Thier, 2008a; Materna, Dicke, & Thier, 2008b). Materna, Dicke, and Thier (2008a) designed an fMRI task in which participants were instructed to use either eye gaze direction or the color of the irises in the eyes to redirect their attention to an object in space. The physical properties of both conditions were identical, thus participants perceived changes in eye gaze – a socially relevant stimulus – in all conditions. However, whether or not participants used the social cue to redirect their attention differed between conditions. Results demonstrated that specific activations in bilateral pSTS were associated with attention shifts based on the social cue of eye-gaze direction and provided evidence that the pSTS is sensitive to the context in which social cues occur.

In addition to responding to biological motion, the right pSTS is also active during viewing of static images of implied human action/motion (Peuskens, Vanrie, Verfaillie, & Orban, 2005). Other studies have implicated the pSTS in processing more general perceptual cues of agency beyond biological motion. Blakemore et al. (2003) found that the left pSTS was active during the viewing of animate-contingent motion of geometric shapes when participants were explicitly directed to attend to the contingent or non-contingent relationships among shapes. Additionally, Lahnakoski and colleagues (2012) examined brain activations during the viewing of film clips that displayed either social or nonsocial features. Film clips were rated according to how well they represented each of eight social features (biological motion, human bodies, faces, pain, emotion, speech, goal-directed actions, and social interaction) and each of six nonsocial features (non-goal-directed action, nonhuman sounds, people not in social interactions, rigid motion, places, and objects). The pSTS showed reliable activations to all eight social features. Functional connectivity analyses indicated that the pSTS region is linked with more specialized circuits in the brain that are more finely tuned to specific forms of social signals and

that respond differentially to the eight social features in the study (Lahnakoski et al., 2012).

Taken together, these results suggest that at least one role of the pSTS is to detect cues of

agency, biological motion, and socially relevant signals within social contexts that are integral to

mentalizing.

The broader area known as the TPJ, defined as the junction of the posterior temporal

gyrus with the parietal cortex, is a heteromodal association cortex that receives input from the

lateral and posterior thalamus, sensory regions, and limbic areas (Decety & Lamm, 2007).

Additionally, this area has reciprocal connections with prefrontal cortex and the temporal lobes.

Hemispheric asymmetry is noted in the literature on the role of the TPJ in cognitive processes

(e.g., Aichhorn et al., 2008). The right TPJ is involved in a variety of social cognitive functions,

including the determination of agency, empathy, and mentalizing (Decety & Lamm, 2007). The

left TPJ has also been implicated in both affective and cognitive mentalizing (Atique, Erb,

Gharabaghi, Grodd, & Anders, 2011), with differences in the strength of activation relative to the

right TPJ dependent on task (Aichhorn et al., 2008). Additionally, the TPJ is highlighted as a

critical brain region for differential processing of information regarding the self versus others

(Lombardo et al., 2010) and is implicated in the production of one's sense of bodily self due to

its integration of vestibular, visuospatial, and other internal signals (Blanke & Arzy, 2005;

Blanke et al., 2005).

The right TPJ is also active during lower-level cognitive processes, such as the broader

ability to reorient attention to behaviorally salient stimuli (Astafiev, Shulman, & Corbetta, 2006;

Shulman et al., 2010) and during violations in expectations of the location of physical stimuli

(Corbetta & Shulman, 2002). In regard to its role in attention, the right TPJ is a component of a

proposed ventral frontoparietal attention network (Corbetta, Patel, & Shulman, 2008). The

ventral attention stream is a bottom-up processing system that detects behaviorally relevant stimuli in the environment. This system interacts with a dorsal frontoparietal network – a top-down control system that attends to sensory stimuli based on internal goals (Corbetta et al., 2008).

To provide a parsimonious account for the involvement of the TPJ in both lower and higher order cognitive processes, Decety and Lamm (2007) suggested that the function of the TPJ might be "generating, testing, and correcting internal predictions about external sensory events" (p. 583). Atique and colleagues (2011) offered a modified version of this claim and suggested that the TPJ has evolved distinct subregions that serve specific functions, including the detection of relevant changes in the environment and the distinction of the self from other agents. What is clear from the research is that the TPJ plays a critical role in the integration of multisensory information and in the attention systems of the brain – two features that support its involvement in the higher cognitive processes involved in mentalizing. In the context of mental state representation, the TPJ may be critical for attention shifts between internal cues and self-oriented perspectives and external cues and other-oriented perspectives (Corbetta et al., 2008). Additionally, van Veluw and Chance (2014) conducted an activation likelihood estimation (ALE) meta-analysis (for review of method, see Turkeltaub, Eden, Jones, & Zeffiro, 2002) of the neurobiological substrates of the perception of self and others and found that the TPJ was involved in both types of perception. In line with this data, Abu-Akel and Shamay-Tsoory (2011) described the TPJ as the initial processor of both cognitive and affective mental states as well as the brain region involved in differentiating self versus other mental states.

The broader STS region and the PCC/PCun are two additional areas that participate in cognitive and affective mentalizing. These regions play key roles in differentiating between self

and other mental states, with the STS involved in processing the mental states of others and the PCC/PCun primarily involved in processing self-referential mental states (Abu-Akel & Shamay-Tsoory, 2011). While the pSTS/TPJ regions play key roles in directing one's attention back and forth from internal cues to social cues in the environment, the broader STS region is specifically involved in processing social cues relevant for other-oriented mentalizing. The STS region (i.e., the cortex within the STS, adjacent cortex in the superior temporal gyrus [STG] and medial temporal gyrus [MTG], and adjacent cortex in the angular gyrus) in both hemispheres is considered to be the major hub for the processing of social perceptual cues (Allison, Puce, & McCarthy, 2000). Allison and colleagues (2000) reviewed early studies on this region in macaque monkeys and more recent neurophysiological and neuroimaging data in humans that demonstrated the role of the STS in processing biological motion, including movements of the eyes, mouth, hands, and body. As previously discussed, such cues are integral to predicting the mental states of other individuals.

In contrast, the PCC/PCun has been shown to be active during tasks that require self-referential processing (e.g., Lou et al., 2004). However, the specificity of PCC/PCun activity to self-referential tasks has been challenged by studies that demonstrate its involvement in processing mental states of others (e.g., Lombardo et al., 2010). In a review of the role PCC, Brewer, Garrison, and Whitfield-Gabrieli (2013) suggested that the PCC may be involved in generating the feeling of being "caught up" in an internal experience, which may or may not directly involve self-referential information. Despite this mixed evidence, Abu-Akel and Shamay-Tsoory (2011) identified this region as important for the representation of cognitive and affective mental states related to the self.

In Abu-Akel and Shamay-Tsoory's model, the TPJ/pSTS, STS, and PCC/PCun are components of both neural networks for cognitive and affective mentalizing. Mental states are first detected in the TPJ, and relevance to the self or to others is determined through the interaction of the dorsal frontoparietal and ventral frontoparietal attention streams. Representations that are tied to other individuals are processed by the pSTS and broader STS region, whereas representations of internal/self mental states are sent through the IPL to the PCC/PCun. Activity in limbic and paralimbic structures, including the anterior cingulate cortex (ACC), temporal pole (TP), striatum, and amygdala, signals whether mental states are cognitive or affective in content. The ACC, TP, and striatum may be anatomically divided into dorsal and ventral parts, and this division is significant for the involvement of each of these areas in both forms of mentalizing. The dorsal parts of these regions subserve cognitive mentalizing, whereas the ventral parts of these regions and the amygdala subserve affective mentalizing. A review of these regions is presented next.

The TP, the most rostral part of the temporal lobe, is consistently implicated in mentalizing tasks (Frith & Frith, 2003) and is activated by both affective content (e.g., Ruby & Decety, 2004) and cognitive content (e.g., Gallagher, Happé, Brunswick, Fletcher, Frith, & Frith, 2000). Olson, Plotzker, and Ezzyat (2007) reviewed literature examining the role of the TP in social and emotional processing and concluded that the TP plays a major role in binding highly processed sensory information with visceral emotional responses and may also contribute to processing social information in the context of a social narrative (i.e., not simply responding to social signals, but responding to social signals embedded in a social context).

Abu-Akel and Shamay-Tsoory (2011) suggested that the dorsal and ventral parts of the TP are involved in processing cognitive and affective mental states, respectively. The authors

based this hypothesis on anatomical studies of the TP in nonhuman primates (i.e., Kondo, Saleem, & Price, 2003). Kondo and colleagues (2003) found that dorsal TP had reciprocal connections with medial prefrontal cortex (MPFC) and the ventral TP had reciprocal connections with the orbitofrontal cortex (OFC) in macaque monkeys. Activity in the OFC is related to affective mentalizing (e.g., Shamay-Tsoory & Aharon-Peretz, 2007; Shamay-Tsoory, Harari, Aharon-Peretz, & Levkovitz, 2010) whereas activity in the MPFC is associated with cognitive mentalizing (e.g., Döhnel et al., 2012). Recent work that examines the connectivity of the TP in humans reveals a more complex picture. Fan and colleagues (2013) used diffusion tensor imaging (DTI) and resting state functional connectivity analyses to divide the TP into three anatomically and functionally distinct subregions: dorsal TP, medial TP, and lateral TP. The latter two subregions were located in the ventral part of the TP. The lateral TP demonstrated the strongest connections with MPFC, whereas the medial TP had connections to the ventral MPFC and OFC. The dorsal TP had strong connections with the inferior frontal gyrus, insular cortex, STG, and MTG. Although these connectivity patterns suggest that the dorsal/cognitive and ventral/affective division may not be appropriate, different regions in the TP are likely engaged during cognitive versus affective mentalizing.

The striatum, the input component of the basal ganglia, is divided into a dorsal region containing the caudate nucleus and putamen and a ventral region containing the nucleus accumbens (Purves et al., 2008). Although less attention has been given to this subcortical structure in the social cognition literature, multiple neuroimaging studies of mentalizing have reported activity in this region (e.g., Baron-Cohen et al., 1999; Brüne et al., 2008). Given the role of the striatum in multiple cortical-subcortical neural circuits that underlie higher cognitive processes (see Koziol & Budding, 2009), the activity of the striatum in mentalizing is expected.

Abu-Akel and Shamay-Tsoory (2011) postulated that the dorsal striatum is involved with

cognitive mentalizing while the ventral striatum is involved with affective mentalizing. Support

for this claim is drawn from research on neurodegenerative processes, particularly those

associated with Parkinson's disease (PD), and their associated cognitive changes. In the early

stages of PD, the dorsal striatum is severely affected by the loss of dopaminergic innervation

from the substantia nigra (MacDonald et al., 2011). As the disease progresses, frontostriatal-

limbic circuitry, including the ventral striatum, is also impacted (Bodden et al., 2010; Zgaljardic

et al., 2006). Mirroring this progression, difficulties in specific forms of mentalizing in

individuals with PD have different times of onset. Impairments in cognitive mentalizing occur in

the early to moderate stages of PD when the disease process affects predominantly dorsal

striatum, while difficulties in affective mentalizing begin to emerge in later stages of the disease

as the ventral striatum is impacted (Poletti, Enrici, & Adenzato, 2012).

The ACC is another region that is active during mentalizing tasks (e.g., Döhnel et al.,

2012). Historically, the ACC was associated with emotion processing, but more recent evidence

suggests that specific divisions of the ACC contribute to cognitive and affective processes (Bush,

Luu, & Posner, 2000). Bush and colleagues (2000) provide a succinct summary of the evidence

for this differentiation with the ACC. The dorsal ACC (dACC) has strong reciprocal connections

with prefrontal cortex, parietal cortex, and premotor and supplementary motor areas and is active

during a variety of cognitive process, including error detection and response selection. In

contrast, the ventral ACC (vACC) has connections with the amygdala, OFC, anterior insula, and

hypothalamus and plays a role in emotion regulation and detecting relevant

emotional/motivational information. Abu-Akel and Shamay-Tsoory (2011) suggested that this

division might extend to mentalizing abilities, with the dACC and vACC processing cognitive and affective mental states, respectively.

The last limbic region discussed within the neuroanatomical model of mentalizing is the amygdala. A large body of literature confirms the role of the amygdala in processing emotions, social behavior, and reward learning (see Adolphs, 2010 for a review), and this region is often active during mentalizing tasks that require emotion recognition and processing affective information (Abu-Akel & Shamay-Tsoory, 2011). For these reasons, the amygdala is included in the model as an area that is specifically involved in affective mentalizing.

Once cognitive and affective mental states are processed in the limbic and paralimbic regions, this information is sent to prefrontal regions to guide "execution/application" decisions (p. 2981; Abu-Akel & Shamay-Tsoory, 2011). Many researchers have identified specific prefrontal cortex regions as crucial for mentalizing, with some proposing that the OFC is a key area (e.g., Stone, 2000) and others emphasizing the importance of MPFC (e.g., Frith & Frith, 2006). According to Abu-Akel and Shamay-Tsoory (2011), cognitive mental states are processed in the dorsal medial prefrontal cortex (dMPFC) and sent to the dorsal lateral prefrontal cortex (dLPFC) while affective mental states are processed in the ventral medial prefrontal cortex (vMPFC) and OFC and sent to the inferior lateral frontal cortex (ILFC). These prefrontal regions allow individuals to utilize mental state information to adapt their behavior and predict the behavior of others.

1.3   DISRUPTIONS OF MENTALIZING IN AUTISM SPECTRUM DISORDER

Although impairments in mentalizing abilities are associated with multiple neurodevelopmental and neurodegenerative disorders (for a review, see Kennedy & Adolphs, 2012), including schizophrenia (Bora & Pantelis, 2013) and frontotemporal dementia (Snowden

et al., 2003; Bertoux, Funkiewiez, O'Callaghan, Dubois, & Hornberger, 2013), deficits in

mentalizing appear to contribute to the core diagnostic features of autism spectrum disorder

(ASD; Tager-Flusberg, 2007). In the Diagnostic and Statistical Manual of Mental Disorders, 5th

edition (DSM-5), ASD is characterized by impairments in social communication and the

presence of stereotyped or repetitive patterns of behaviors or interests (American Psychiatric

Association, 2013). ASD is one of the most common neurodevelopmental disorders, affecting

approximately 1 in 68 children in the United States (Centers for Disease Control and Prevention,

2014).

Individuals with ASD demonstrate impairments in both cognitive and affective

mentalizing (e.g., Brent, Rios, Happé, & Charman, 2004; Klin, 2000). For example, Brent and

colleagues (2004) compared the performances of school-aged children with ASD to typically

developing children matched on language age equivalents on three mentalizing tasks: the Strange

Stories test (Happé, 1994; Happé, Winner, & Brownell, 1999), the Cartoons task (Happé et al.,

1999), and the Reading the Mind in the Eyes task (Baron-Cohen et al., 2001). The Strange

Stories test and the Cartoons task tap into cognitive mentalizing while the Reading the Mind in

the Eyes task taps into affective mentalizing. Youth with ASD performed significantly worse on

the Strange Stories test and the Reading the Mind in the Eyes task than the typically developing

children. Another study by Klin (2000) compared the number of cognitive and affective mental

state attributions produced by adolescents and adults with and without ASD to explain videos of

animated geometric shapes. Individuals with ASD produced significantly fewer cognitive and

affective mental state attributions compared to typically developing individuals. Abell, Happé,

and Frith (2000) also utilized videos of animated geometric shapes (triangles) to examine

mentalizing abilities in four groups: 1) children with ASD, 2) children with general intellectual

impairment, 3) typically developing children matched on verbal mental age to the two clinical groups, and 4) adults. Three categories of videos were used: Random (triangles moved randomly around the screen), Goal-Directed (movement of triangles portrayed one "character" acting in response to another "character's" behavior, such as chasing or fighting), and Theory of Mind (ToM; movement of triangles portrays one "character" responding to the mental state of another "character," such as surprising and coaxing). Abell and colleagues (2000) also measured mentalizing abilities through standard false belief tasks. These tasks are more structured than the animated videos and have dichotomous answer options (i.e., correct or incorrect). Although children with ASD performed as well as the other two groups of children on standard false belief tasks, differences emerged in regard to their descriptions of the ToM videos. Children with ASD used fewer mental state terms to describe ToM videos than typically developing children and adults and used a higher number of inaccurate mental state terms to describe the videos compared to the other groups. These results suggest that individuals with ASD, particularly those with cognitive abilities in the average or above range, may be able perform in the expected range on structured mentalizing tasks yet still demonstrate difficulties with "online" mentalizing.

Researchers have begun to explore the neural correlates of mentalizing deficits in individuals with ASD, and results demonstrate atypical activations in brain regions within the proposed mentalizing network. Individuals with ASD show reduced areas of activation in pSTS/TPJ (Kana, Libero, Hu, Deshpande, & Colburn, 2014), reduced functional specialization of right TPJ (Lombardo, Chakrabarti, Bullmore, MRC AIMS Consortium, & Baron-Cohen, 2011), abnormal functional specialization of the medial rostral PFC (Gilbert, Meuwese, Towgood, Frith, & Burgess, 2009), and hypoactivation of the left superior medial frontal gyrus, left anterior paracingulate cortex, bilateral ACC, and left OFC (Kana, Keller, Cherkassky,

Minshew, & Just, 2009) during mentalizing tasks. Other studies of social cognition in ASD have shown decreased or atypical activation of the amygdala (Baron-Cohen et al., 1999; Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004) and striatum (Baron-Cohen et al, 1999).

Although ASD is a distinct clinical disorder, a broader spectrum of "autism traits" (i.e., difficulties with social communicative behaviors) exists in the general population (Constantino & Todd, 2003; Robinson et al., 2011). This dimensional approach holds that ASD represents one extreme end (i.e., deficit) of the spectrum of social cognitive abilities in the population. Constantino and Todd (2003) provided strong evidence to support this idea by examining the distribution and genetic structure of autism traits in 788 pairs of twins drawn from a larger epidemiological study. They found that social communicative behaviors were "1) common; 2) continuously distributed; 3) moderately to highly heritable; 4) influenced by the same additive genetic factors in boys and girls; and 5) exhibit no evidence of nonadditive genetic factors" (p. 528). Subsequent studies and reviews examining autism traits in relatives of individuals with ASD (e.g., Sucksmith, Roth, & Hoekstra, 2011) and in the general population (e.g., Robinson et al., 2011) have also shown these traits to be distributed along a continuum.

Given that autism traits seem to be distributed in the general population and individuals with ASD demonstrate atypical brain activations consistent with the proposed neural network for mentalizing, understanding the neural correlates of mentalizing dysfunction in ASD is informative for developing a fuller account of "typical" social cognitive function. Conversely, knowledge of the neural mechanisms of mentalizing in neurotypical adults provides a framework through which to explore dysfunctions in mentalizing in ASD. The proposed project aims to utilize such a reciprocal approach to evaluate the role of white matter in mentalizing and self-reported autism traits in neurotypical adults.

1.4   WHITE MATTER TRACTS AND MENTALIZING

As discussed earlier, the various roles of grey matter regions in social cognition and mentalizing in clinical and non-clinical populations have been explored in depth by numerous studies. Less attention has been given to illuminating the role of white matter pathways in these cognitive abilities. A brief review of white matter tracts involved broadly in social cognition and specifically in ASD is provided next.

White matter refers to myelineated axonal fibers that function as communicative pathways among neurons. Advances in MRI technology have made it possible to study patterns of typical and atypical white matter microstructure in vivo (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Bassett, Brown, Deshpande, Carlson, & Grafton, 2011). Such data are of increasing importance given that cognitive processes are understood to arise from the coordinated activity of multiple cortical and subcortical networks in the brain (Bassett & Gazzaniga, 2011; Bullmore et al., 2009; Koziol & Budding, 2009).

Diffusion tensor imaging (DTI), a type of MRI, allows for the measurement of white matter in the brain based on different rates and directions of diffusion of water molecules through tissue types (Soares, Marques, Alves, & Sousa, 2013). One common measure of white matter derived from DTI is fractional anisotropy (FA), which corresponds to whether water molecule diffusion is isotropic (i.e., in all directions equally) or anisotropic (i.e., along one axis; Soares et al., 2013). FA values range from 0 to 1, with 0 indicating diffusion equally in all directions and 1 indicating diffusion in along a single axis. Water diffusion tends to be isotropic in grey matter and cerebrospinal fluid, whereas water diffusion in white matter tends to be directionally dependent on the orientation of the white matter pathway (Hagmann et al., 2006).

The model proposed by Abu-Akel and Shamay-Tsoory (2011) provides a valuable framework for considering the role of white matter tracts in mentalizing. Although the model does not include an in-depth review of white matter tracts connecting brain regions involved in mentalizing, it does provide a springboard for identifying candidate tracts within the mentalizing network. Literature on white matter disruptions in ASD is also informative since mentalizing abilities are often noted in individuals with ASD and hypothesized to be at least partially responsible for the core deficits of ASD (Baron-Cohen, Leslie, & Frith, 1985; Tager-Flusberg, 2007). Two white matter tracts that appear likely to be implicated in the neural network for mentalizing are the uncinate fasciculus (UF) and the inferior longitudinal fasciculus (ILF).

The UF is a ventral associative bidirectional tract that connects the anterior temporal lobe (including TP) to the medial and lateral OFC and anterior prefrontal cortex (Catani & Thiebaut de Schotten, 2008; Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012). Given its proximity to limbic structures including the amygdala (Thiebaut de Schotten et al., 2012), the UF is often associated with the limbic system (Von Der Heide, Skipper, Klobusicky, & Olson, 2013). The UF connects multiple regions in the mentalizing network proposed by Abu-Akel and Shamay-Tsoory (2011), including the TP, amygdala, and OFC. Von Der Heide and colleagues (2013) reviewed literature on the anatomy of the UF and its role in various neurological and psychiatric disorders. They suggested that the UF "allows temporal lobe-based mnemonic representations (e.g., a person's name + face + voice + your feelings about a person) to modify behavior by interacting with systems in the lateral OFC that are instrumental for making associations between stimuli and rewards, and ultimately, decision making" (p. 1701).

Multiple DTI studies have identified disruptions in the UF in individuals with ASD (e.g., Barnea-Goraly, Lotspeich, & Reiss, 2010; Kumar et al., 2010; Poustka et al., 2012; Pugliese et

al., 2009). For example, Poustka et al. (2012) found lower FA values in bilateral UF in children

with ASD compared to typically developing children matched on age, sex, and IQ. Noriuchi and

colleagues (2010) also found reduced FA values in the TP/amygdala region in school-aged

children with ASD, and these results may reflect disruptions in the UF. Relatedly, a study by

Elison and colleagues (2013) linked the UF to joint attention – the ability to orient one's

attention to distal objects of interest based on visual cues of another person. A lack of joint

attention is an early behavioral marker of ASD (Charman, 2003). Elison et al. (2013) found that

FA values in the right UF in 6-month-old typically developing infants predicted joint attention

performance (i.e., the ability to orient one's attention to objects of interest based on visual cues

of another person) in those infants at age 9 months. Taken together, this evidence supports the

role of the UF in the symptomology of ASD and in mentalizing abilities.

The ILF is a ventral associative tract running from the occipital lobe up through the TP

(Catani & Thiebaut de Schotten, 2008; Mori, Wakana, Nagae-Poetscher, & van Zijl, 2005). The

ILF has been associated with visual memory (Shinoura et al., 2007) and object recognition

(Ortibus et al., 2011). Fox, Iaria, and Barton (2008) speculated that the ILF might have a specific

role in facial recognition based on its connections between visual processing areas and memory

areas in the brain. More generally, the ILF may be important for bringing visual information to

the temporal lobe.

The ILF is another white matter tract that appears disrupted in ASD (e.g., Jou et al., 2011;

Kana et al., 2014; Koldewyn et al., 2014; Pugliese et al., 2009). For example, Kana and

colleagues (2014) found reduced FA values in the right ILF in adolescents and adults with ASD

compared to typically developing individuals matched on age and IQ. In another recent study,

Koldewyn and colleagues (2014) found that the right ILF was the only white matter tract with

lower FA values in children with ASD compared to typically developing children after carefully controlling for motion artifacts in the scans. These studies suggest that the ILF is genuinely disrupted in ASD and potentially related to disruptions in sensory input to the mentalizing network.

In addition to examining white matter disruptions in individuals with ASD, researchers also have started to examine relationships between white matter and self-reported autism traits in neurotypical individuals. One recent study by Iidaka, Miyakoshi, Harada, and Nakai (2012) took a step in this direction by examining the white matter between two brain regions implicated in social cognition and ASD, the STS and amygdala, and its relation to self-reported autism traits in neurotypical adults. This study included 30 neurotypical undergraduate students, graduate students, and post-doctoral fellows. Participants completed the Autism-Spectrum Quotient (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) as a measure of self-reported autism traits, fMRI tasks to identify the STS and amygdala, and DTI scans. Iidaka and colleagues used probabilistic tractography to examine white matter connecting the STS and amygdala and used correlational analyses to evaluate the relationship between the volume of white matter connectivity and AQ total scores. They found that a higher volume of connectivity in the left ILF positively correlated with self-reported autism traits, even though the traits were below the clinical threshold in this non-clinical sample. The volume of connectivity is a different measure of white matter than FA values, and thus it is difficult to compare the results of this study to studies of FA values in the ILF in individuals with ASD. However, this study suggests that self-reported autism traits are associated with differences in white matter in neurotypical adults.

1.5   THE CURRENT STUDY

The literature reviewed so far provides substantial evidence for 1) brain regions involved in the mentalizing network in neurotypical individuals, 2) disruptions in mentalizing as common behavioral markers of ASD, 3) disruptions in brain regions associated with mentalizing in ASD, and 4) the validity of conceptualizing autism traits and related behaviors as distributed throughout the general population. Taken together, this literature suggests that uncovering specific relationships among autism traits, mentalizing abilities, and neural networks will be informative for understanding typical and atypical forms of mentalizing. The study by Iidaka and colleagues (2012) provides a valuable example of utilizing this approach because they related measurements of white matter to self-reported ASD traits in neurotypical adults. However, this study did not include a specific measure of mentalizing abilities and used a measure of white matter (i.e., volume connectivity) that does not directly correspond to the commonly reported FA values in studies examining white matter in individuals with ASD. The current study expanded on the approach used by Iidaka and colleagues (2012) by examining relationships among white matter FA values for white matter tracts based on a neuroanatomical model, mentalizing abilities, and self-reported ASD traits in neurotypical adults.

The majority of the reviewed research on the neural underpinnings of mentalizing focuses on grey matter regions, and few studies examine the role of specific white matter tracts in the mentalizing network. The current study contributed to filling this gap by examining the relationships among white matter microstructure, self-reported autism traits, and mentalizing abilities in neurotypical adults. Two specific white matter tracts, the UF and ILF, were the focus of the current study because they connect regions within and/or provide sensory information to the proposed mentalizing network by Abu-Akel and Shamay-Tsoory (2011). This model-based

approach is useful for guiding hypotheses and interpreting results. Additionally, disruptions in these two tracts have been identified in multiple studies of individuals with ASD (e.g., Poustka et al., 2012; Pugliese et al., 2009), and the ILF has been implicated in autism traits in neurotypical individuals (Iidaka et al., 2012).

1.6   SPECIFIC AIMS AND HYPOTHESES

Specific Aim 1: The first aim of this project was to evaluate the relationship between self-reported autism traits and a measure of mentalizing in neurotypical adults.

Hypothesis 1a: Higher levels of self-reported autism traits would be associated with lower levels of mentalizing.

Specific Aim 2: The second aim of this project was to evaluate the relationship between self-reported autism traits and the microstructure of white matter tracts, using fractional anisotropy (FA), that are likely to be involved in the mentalizing network, specifically the UF and ILF, in neurotypical adults. Although Iidaka and colleagues (2012) found a positive relationship between white matter volume in the left ILF and levels of self-reported autism traits, we expected that higher levels of self-reported autism traits would be associated with lower FA values in the UF and ILF given that previous research on white matter disruptions in ASD found this relationship (e.g., Poustka et al., 2012; Pugliese et al., 2009). Our measure of white matter microstructure (i.e., FA values) differs from the measure of white matter volume used by Iidaka and colleagues (2012), and we expected that this difference in methodology might also lead to a different pattern of results. To test the specificity of these relationships, we included a tract outside of the mentalizing network – the corticospinal tract (CST) – in our analyses. The CST is one of five major tracts in the brainstem and descends from the cortex (primarily motor cortex)

through the cerebral peduncle (Mori et al., 2005). The CST is important for motor control (Kim et al., 2008) and was not hypothesized to be involved in the mentalizing network.

Hypothesis 2a: Higher levels of autism traits would be associated with lower FA values in the UF.

Hypothesis 2b: Higher levels of autism traits would be associated with lower FA values in the ILF.

Hypothesis 2c: Levels of autism traits would not be associated with FA values in the CST.

Specific Aim 3: The third aim of this project was to evaluate the relationship between mentalizing and the microstructure of white matter tracts (FA values) that are likely to be involved in the mentalizing network (i.e., UF, ILF) in neurotypical adults. We expected that mentalizing abilities would be positively associated with FA values in the UF and ILF given that these tracks connect brain regions within the mentalizing network proposed by Abu-Akel and Shamay-Tsoory (2011). To test the specificity of these relationships, we included the CST as a control tract in our analyses.

Hypothesis 3a: Poorer performance on a mentalizing task would be associated with lower FA values in the UF.

Hypothesis 3b: Poorer performance on a mentalizing task would be associated with lower FA values in the ILF.

Hypothesis 3c: Performance on a mentalizing task would not be associated with FA values in the CST.

2 METHOD

2.1 PARTICIPANTS

A total of 25 individuals participated in this archival study at Georgia State University (GSU) and were recruited as part of a larger project to validate a new set of stimuli for a mentalizing task appropriate for use in fMRI studies (Principal Investigator: Diana L. Robins). The current study used data gathered as part of this larger project and did not involve additional visits or measures. The Georgia State University/Georgia Institute of Technology Joint Center for Advanced Brain Imaging Institutional Review Board (IRB: H11247) approved this study. All participants provided informed consent.

All participants met the following inclusion criteria: 1) typically developing, 2) right-handed, and 3) between the ages of 18 to 25 years. Exclusion criteria included: 1) contraindications for MRI procedures (e.g., metal in the body, dental braces), 2) medical or mental health issues related to neurological disease and psychiatric, developmental, or perceptual disabilities, and 3) cognitive abilities estimated to be more than two standard deviations from the mean on standardized testing. We recruited participants online from the undergraduate participant pool at Georgia State University and by flyers and word of mouth among the GSU community and in the metro-Atlanta area.

We excluded one participant's data from the larger study and the current study because that individual had a brain abnormality identified during the structural MRI scan. We conducted initial quality control procedures for the structural MRI data for the remaining 24 participants. These procedures included visual inspection of T1-weighted structural images and FA images for motion and acquisition artifacts and visual inspection of DTI color maps for major distortions of fiber orientations. All 24 participants had usable DTI data for analyses. The mean age at the time

of study participation was 21.92 (SD = 4.72) years. Ages ranged from 18.37 years to 25.58 years.

Fifteen of the 24 participants were female (62.5%). Participants self-identified their racial/ethnic

background as follows: Caucasian = 9 individuals (37.5%), African American = 9 individuals

(37.5%), Asian American = 1 individual (4.17%), Multiracial = 5 individuals (20.83%). Out of

the 24 participants, two individuals (8.33%) identified also as Hispanic/Latino.

2.2   MEASURES

2.2.1   *Mentalizing*

The Dynamic Interactive Shape Clips (DISC) are a novel set of stimuli designed to

measure cognitive and affective mentalizing. The DISC stimuli consist of animated clips of

geometric shapes (i.e., one circle, one triangle, and one square). Each clip has a duration of 10

seconds. In addition to the geometric shapes, some clips also contain static "props," including a

large opaque gray square, a green "hill" that slopes upward toward the right, and an empty large

rectangle that has a "door" (i.e., one slide moves back and forth). Clips with props contain one

static prop, and the geometric shapes appear to "use" or "climb on" the props (see Figure 2.1).

Additionally, some clips contain one or more shapes that appear to change size (i.e., grow bigger

or smaller then return to original size). For some DISC trials, participants were instructed to

attend to size changes in the clips. These size changes serve two purposes: 1) to ensure that

participants are paying attention to the shapes and accurately report how many shapes did or did

not change size and 2) to evaluate whether directing the participants' attention to physical

qualities of the stimuli altered the extent to which they engaged in mentalizing while viewing the

clips. These clips were created using Adobe Flash (Adobe, 2011 version) and were presented on

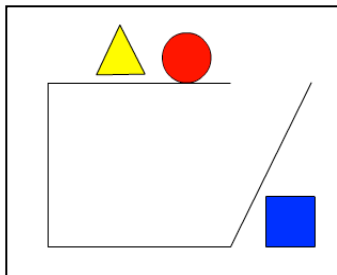a computer using DirectRT (Jarvis, 2006).

Figure 2.1 Static Image of DISC Stimulus

There are two main types of clips: Social DISC and Random DISC. Social DISC are designed to convey social interactions based solely on basic movement cues of the geometric shapes. Previous research has demonstrated that typically developing individuals perceive social interactions among objects and attribute thoughts, emotions, and personality characteristics to objects when specific types of movement cues are present (Blakemore et al., 2003; Heider & Simmel, 1944; Klin, 2000). These movement cues include social contingency between objects (i.e., one object appears to change the course of its movement based on the motion of another object due to the timing of motion changes) and animacy (i.e., motion that includes Non-Newtonian changes in direction and speed; Blakemore et al., 2003; Heider & Simmel, 1944). Klin (2000) argued that this type of task assesses mentalizing while also minimizing factors that promote performance on other mentalizing tasks that are absent in real-life social situations. For example, studies have shown that performance on some mentalizing tasks positively correlates with level of verbal skills (e.g., Yirmiya, Erel, Shaked, Solomonica-Levi, 1998). Given that numerous mentalizing tasks are presented in a verbal format, it is unsurprising that higher verbal abilities would be related to better task performance. Stimuli such as the DISC minimize this confound by using nonverbal stimuli. In contrast to the Social DISC, Random DISC are designed to minimize the perception of animate and contingent motion. These clips show the three geometric shapes moving at a constant speed around the screen. When a shape reaches the

edge of the screen, it "bounces" off the edge and continues at the same speed in a new linear direction. Both types of DISC contain shapes that change size.

Within the Social DISC, there are three types of social interactions: Approach, Aggress, and Avoid. Approach clips show the geometric shapes in positive social interactions by having one or more shapes move toward another shape. The "approached" shape reciprocates that movement by moving toward the "approaching" shape(s) or by "waiting" (i.e., remaining static) for the "approaching shape" to reach it. An example of an Approach clip shows one shape "helping" another shape by "pushing" it up a "hill." Aggress clips show one or more shapes in negative social interactions with another shape by having one or more shapes actively "hinder" the movement of another shape. An example of an Aggress clip shows one shape "hindering" a second shape by repeatedly "pushing" the second shape down the hill. Finally, Avoid clips show one or more shapes "disengaging" from social interactions by having these shapes continually move away from another shape. An example of an Avoid clip shows one shape continually moving away from the two other shapes as they "follow" it.

The DISC were created to be used as stimuli for fMRI studies and may also be used in behavioral studies of mentalizing (Robins et al., in prep). For the purposes of this project, the data from the behavioral administration of the DISC was used. The behavioral administration of the DISC occurred immediately after the MRI scans were completed by participants. The behavioral administration consisted of two runs of DISC, and each run contained nine clips. Run 1 contained two Random DISC, three Social-Aggression DISC, three Social-Approach DISC, and one Social-Avoid DISC. Run 2 included two Random DISC, one Social-Aggression DISC, three Social-Approach DISC, and three Social-Avoid DISC. The order of clips in each run was

pseudorandomized. Participants were randomly assigned to complete Run 1 followed by Run 2 or Run 2 followed by Run 1.

Prior to each clip, one of three cue words was displayed on the computer screen for two seconds: WATCH, FRIENDS, or SIZE. Two types of responses were collected following each clip: forced-choice responses to four questions and verbal responses to the open-ended prompt, "Describe the movie." The first two forced-choice questions changed depending on the cue prior to the movie. The cue words served to direct the participants' attention to specific features of the clips and alert the participants to the type of forced-choice questions they were asked to answer. The "WATCH" cue was the most open-ended cue, and was followed by forced-choice questions asking the participants to 1) "Push a button" and 2) "Push the other button." This cue was only used for Random DISC. These questions provided a measure of participants' attention. The "FRIENDS" cue directed participants' attention to the social nature (if any) of the clips and was followed by two forced-choice questions: 1) "Were any friends?" and 2) "Were any not friends?" The "SIZE" cue directed participants' attention to the physical qualities of the shapes and was followed by two different forced-choice questions: 1) "Did any change size?" and 2) "Did any not change size?" After these two forced-choice questions, the open-ended prompt "Describe the movie" appeared on the screen. Participants provided oral responses to this prompt which were audio-recorded and transcribed by trained research assistants. The open-ended prompt remained on the screen until the participants hit the spacebar on the keyboard. This allowed the participants to provide oral responses to the prompt with as much time as they needed. The last two forced-choice questions were the same for each clip and appeared after the oral responses to the open-ended prompt were finished. Participants were asked to rate each clip on a 1-9 scale for

valence (1 = very positive, 5 = neutral, 9 = very negative) and intensity (1 = very intense, 5 = moderate, 9 = very mild).

The transcribed oral responses to the open-ended prompt provided a measure of mentalizing. These responses were coded using a modified coding system based on the Social Attribution Task indices of Klin (2000). Klin (2000) developed an extensive coding system for narratives produced by participants in response to stimuli very similar to the DISC. The Animation Index (AI) was used for this project. The AI provided a summary measure of the overall level of social attribution and mentalizing present in participants' narratives for each clip. Each clip was scored on a 0 to 6 point scale, with 0 indicating an absence of agency and social description and 6 indicating a high level of complex social description. A full description of the coding system for the AI can be found in Appendix A. Two trained coders assigned a score from the AI to each oral narrative for every participant (18 total for each participant). Inter-rater reliability for the coders was good (Intraclass Coefficient = .88). We calculated an average AI score for each oral narrative for every participant from the two AI codes provided by the coders. To create summary scores, we calculated average AI scores for each participant for Social-DISC (i.e., Approach, Aggression, and Avoid) with the FRIENDS cue (seven clips), Social DISC with the SIZE cue (seven clips), and Social DISC across both FRIENDS and SIZE cues (14 clips). We excluded Average AI scores for Random DISC from these summary scores because these clips were not designed to elicit mental state attributions and thus would artificially lower AI scores. We selected the average AI score for Social DISC across both FRIENDS and SIZE cues as our overall measure of mentalizing for each participant, hence called "DISC Mentalizing scores".

2.2.2   Autism Traits

The Autism-Spectrum Quotient (AQ) is a 50-item self-report questionnaire designed to assess traits associated with ASD in adults with average cognitive abilities (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). Each item consists of a statement that describes either a characteristic of ASD (e.g., "I frequently find that I don't know how to keep a conversation going") or a preference associated with ASD (e.g., "I am fascinated by numbers"). Individuals rate the degree to which a statement describes themselves by choosing one of four options: definitely agree, slightly agree, slightly disagree, and definitely disagree. To avoid response bias, approximately half of the items are worded such that an "agree" response indicates a higher level of autism traits whereas the remaining half are worded such that a "disagree" response indicates a higher level of autism traits. Each item to which an individual provides a response associated with a higher level of autism traits is scored 1 point. Six scores are derived from the AQ: a total score (range 0-50) and five subscores (range 0-10). The five subscores measure specific sets of behaviors and skills associated with ASD and were developed based on a priori knowledge of the clinical presentation of ASD: 1) Social Skill, 2) Attention Switching, 3) Attention to Detail, 4) Communication, and 5) Imagination.

To validate the AQ, Baron-Cohen and colleagues (2001) administered the instrument to four groups: 1) 58 adults with ASD, 2) 174 randomly selected healthy adults to act as controls, 3) 840 students at Cambridge University, and 4) 16 individuals who won the UK Mathematics Olympiad. The authors were interested in examining whether an association between science/math skills and autism traits could be identified using this measure, and the students and mathematicians provided data to address that question. Individuals with ASD scored significantly higher on the AQ than matched controls. Average scores did not differ between

randomly selected adults and students, suggesting that cognitive abilities and social economic status do not appear to influence scores on the AQ for individuals with average to above average cognitive abilities. In the control group, men scored significantly higher than women. Finally, individuals in math and computer/physical sciences scored higher than individuals in the humanities and social sciences. The authors determined that a cut-off of 32 was useful for identifying individuals who endorse a level of autism traits similar to individuals with clinical diagnoses of ASD.

In regard to psychometrics, Baron-Cohen and colleagues (2001) examined test-retest reliability by having 17 students from the student group complete the AQ two weeks after the initial administration. The scores between the two time points were not significantly different and were strongly correlated ($r = .70$, $p = .002$). The AQ has demonstrated good discriminative validity for identifying adults with ASD who complete the AQ and then complete a full diagnostic evaluation (Woodbury-Smith, Robinson, Wheelwright, & Baron-Cohen, 2005) and good convergent validity with another screening measure of ASD (Armstrong & Iarocci, 2013). Other versions of the AQ have been developed, including a short form (AQ-Short; Hoekstra et al., 2011). The AQ-Short consists of 28 items from the original 50 items, has similar psychometric properties to the AQ, and correlates very highly with the AQ (Hoekstra et al., 2011).

Given that the AQ was developed based on clinical knowledge of ASD, questions arose as to whether the AQ measured the same traits in the same way across clinical and non-clinical populations (Murray, Booth, McKenzie, Kuenssberg, & O'Donnell, 2013). Although evidence suggests that autism traits are present on a continuum in the general population (e.g., Todd & Constantino, 2003), few studies specifically examined whether tools developed for identifying

ASD are valid for use in non-clinical populations. To address this, Murray and colleagues (2013) compared the AQ-Short in ASD and non-ASD groups using multi-group confirmatory factor invariance analysis. Results indicated that the AQ-Short measures the same latent traits across groups but that caution should be used when making comparisons of levels of autism traits across groups. For the purposes of the current study, the AQ total score appeared to be an appropriate measure of autism traits for neurotypical individuals.

2.2.3   Empathy

The Empathy Quotient (EQ) is a 40-item self-report questionnaire designed to measure empathy in adults of average intelligence (Baron-Cohen & Wheelright, 2004; Allison, Baron-Cohen, Wheelwright, Stone, & Muncer, 2011). Each item describes a behavior or attitude, and individuals rate the degree to which they agree that the item describes themselves by choosing one of four answer options: strongly agree, slightly agree, slightly disagree, strongly disagree. For 19 items, "strongly disagree" is scored as two points and "slightly disagree" is scored as one point. For the remaining 21 items, "strongly agree" is scored as two points and "slightly agree" is scored as one point. Scores range between 0-80 points. Individuals with ASD generally score lower on the EQ compared to neurotypical individuals and the EQ has a significant inverse relationship with the AQ (Baron-Cohen & Wheelwright, 2004). To validate the AQ scores in this typically developing sample, we included the EQ to check for the known association between these measures.

2.2.4   Cognitive Abilities

The Wechsler Abbreviated Scale of Intelligence (WASI) is a short, standardized assessment of cognitive abilities (Wechsler, 1999). The WASI has two administration procedures: a four-subtest option and a two-subtest option. We chose to use the two-subtest

procedure in order to reduce the amount of testing time required for participants. The two-subtest WASI includes Vocabulary, a measure of verbal knowledge, and Matrix Reasoning, a measure of nonverbal reasoning. Subtests scores are provided as T-scores with a mean value of 50 points and a standard deviation of 10 points. These two subtests create a composite score, the Full Scale Intelligence Quotient. The FSIQ is presented as a standard score with a mean value of 100 points and a standard deviation of 15 points.

2.2.5   *Clinical and Adaptive Behavior*

The Behavior Assessment System for Children, Second Edition (BASC-2) is a comprehensive rating system that identifies patterns of maladaptive and adaptive behaviors (Reynolds & Kamphaus, 2004). The BASC-2 has multiple versions for different age ranges. We used the BASC-2 Self-Report of Personality (SRP), College Version, for ages 18-25 years. This version contains 12 clinical scales: Alcohol Abuse, Anxiety, Attention Problems, Atypicality, Depression, Hyperactivity, Locus of Control, School Maladjustment, Sensation Seeking, Sense of Inadequacy, Social Stress, and Somatization. Each of these scales produces a T-score. For the clinical scales, T-scores of 59 or below are Within Normal Limits, T-scores of 60 to 69 are considered At-Risk for problematic behaviors, and T-scores at or above 70 are in the Clinically Significant range of problematic behaviors. The BASC-2 SRP also includes four adaptive scales that produce T-scores: Interpersonal Relations, Relations with Parents, Self-Esteem, and Self-Reliance. For the adaptive scales, T-scores at or above 41 are Within Normal Limits, T-scores between 31 to 40 are considered At-Risk for deficits in adaptive skills, and T-scores at or below 30 are in the Clinically Significant range.

We decided to use one of the BASC-2 clinical scales, specifically the Somatization scale, as a control variable for our analyses. The BASC-2 Somatization scale measures the tendency to

be very sensitive to minor physical problems and discomfort (Reynolds & Kamphaus, 2004). The BASC-2 Somatization scale relies on the same method of assessment as the AQ (i.e., self-report), and it measures a construct that is not thought to be associated with autism traits. This dissociation allows us to tease apart whether any significant effects we observe related to self-reported autism traits are due to the method of assessment or the construct measured.

2.2.6   *White Matter Microstructure and Tracts*

White Matter Integrity. Diffusion tensor imaging (DTI) is a type of magnetic resonance imaging (MRI) that allows for the visualization and measurement of white matter by examining properties of water diffusion in the brain (as reviewed by Soares, Marques, Alves, & Sousa, 2013). The rate and directionality of water diffusion differs based on the architecture, integrity, and type of tissue, and this allows for the estimation of white matter pathways (Soares et al., 2013). Water diffusion tends to occur equally in all directions in grey matter and cerebrospinal fluid (i.e., isotropically), whereas water diffusion in white matter tends to be directionally dependent on the orientation of the white matter pathway (i.e., anisotropic; Hagmann et al., 2006). Numerous measures of white matter microstructure can be derived from DTI data, including the molecular diffusion rate (Mean Diffusivity [MD]), the directional dependence of diffusion (Fractional Anisotropy [FA]), and the diffusion rates along the main axis of diffusion (Axial Diffusivity [AD]) and along the transverse direction (Radial Diffusivity [RD]; Soares et al., 2013). FA values are the primary measure of white matter tracts for the proposed project. FA values range from 0 to 1, with 0 indicating diffusion equally in all directions (i.e., isotropic) and 1 indicating diffusion along one axis (i.e., anisotropic).

Scan Acquisition. All neuroimaging data were collected using a Siemens Trio 3T scanner with a standard RF 12 channel head coil at the Georgia State University/Georgia Institute of

Technology Joint Center for Advanced Brain Imaging. For DTI, we collected a 30- direction

single shot spin echo diffusion-weighted sequence with 60 contiguous axial slices interleaved

and 2 non-diffusion weighted images with 2.0 x 2.0 x 2.0 mm resolution and coverage of the

whole head (b value = 1000s/mm^2, TE/TR=90ms/7700ms, FOV=204mm, GRAPPA parallel

imaging with acceleration factor PE=2). For anatomical registration, we collected whole brain

T1-weighted images (Sagittal 3D MP-RAGE, 1mm^3, TR=2250 ms, TE 3.98 ms, TI=850,

256x256 matrix, GRAPPA parallel imaging with acceleration factor PE=2, 176 slices).

DTI and T1 Data Processing. For an overview of the processing pipeline for the DTI

data, please see the script in Appendix B. We processed the DTI and T1-weighted data using

tools in FMRIB Software Library v5.0 (FSL; Jenkinson, Beckmann, Behrans, Woolrich, &

Smith, 2012) and FMIRB's Diffusion Toolbox (FDT; Behrens et al., 2003). We first converted

DICOM files from the scanner to NIfTI files using the dcm2nii command in Linux. We applied

eddy current correction using FDT to adjust for distortions in images due to eddy currents and

simple head motion. We used the Brain Extraction Tool (BET; Smith, 2002) to remove skull and

non-brain tissue from all whole-head images. We also used FMRIB's Automated Segmentation

Tool (FAST; Zhang, Brady, & Smith, 2001) on the T1-weighted images to correct for spatial

intensity variations and segment the images into different tissue types. We then conducted a

series of linear and nonlinear registrations to ensure that each participant's data in DTI space

corresponded to his/her T1-weighted space and to standard space (MNI152). First, we conducted

a rigid body registration of the data in DTI space to T1-weighted space with six degrees of

freedom using FMRIB's Linear Image Registration Tool (FLIRT; Jenkinson, Bannister, Brady,

& Smith, 2002; Jenkinson & Smith, 2001). Next, we registered data in T1-weighted space to the

MNI152 template with 12 degrees of freedom using FLIRT. We then conducted a nonlinear

registration of data in the T1-weighted space to the MNI152 constrained by the 12 degrees of

freedom linear registration using FMRIB's Nonlinear Image Registration Tool (FNIRT,

Andersson, Jenkinson, & Smith, 2007). We then inverted each of these transformations in order

to provide the reverse mapping from MNI template space to T1-weighted space to DTI space. To

fit a diffusion tensor model and identify the primary direction of diffusion at each voxel, we ran

DTIFIT (part of FDT) on the DTI data. DTIFIT calculates the FA values that we will use for

analyses. As part of our initial quality control procedures, we visually inspected each

participant's color map using FSLVIEW (visualization program in FSL). Each color map

displays the orientation of white matter tracts by assigning color to each of the three main

directions (red = right-left, green = anterior-posterior, blue = inferior-superior; Mori et al., 2005).

We visually inspected each color map to ensure that major fiber bundles were correctly oriented

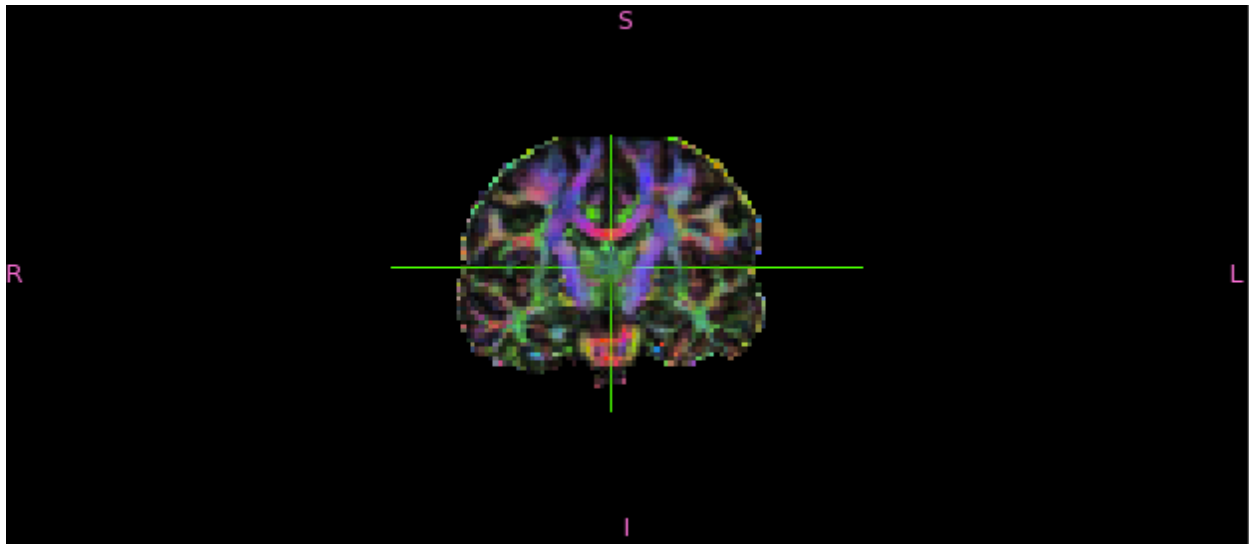(see Figure 2.2 for an example color map).

Figure 2.2 Example Color Map

Examination of FA Values. To examine FA values for each participant, we used Tract-

Based Spatial Statistics v1.2 (TBSS) in FSL (Smith et al., 2006). TBSS creates a mean FA image

from all participants' aligned DTI data; this mean FA image is then thinned to create a mean FA

skeleton that represents to center of all tracts common to the group. Each participant's FA data is then projected onto this skeleton. W used these data for voxelwise cross-participant statistical analyses. We selected TBSS to examine FA values because it increases our certainty that we are comparing FA values in the same tracts across participants through use of data that has undergone careful linear and nonlinear registrations and by focusing analyses to areas of tracts common to all participants. Other researchers have used TBSS to identify white matter differences in single groups of healthy participants with sample sizes similar to ours (e.g., Forstmann et al., 2008; Mayer & Vuong, 2013) and between groups of healthy participants who differ on lifestyle choices with total sample sizes similar to ours (e.g., Tseng et al., 2013).

2.3   PROCEDURE

We collected all data as part of a larger project at GSU and at the Georgia State University/Georgia Institute of Technology Joint Center for Advanced Brain Imaging. Participants completed all study procedures across two visits on different days. During the first visit, participants completed a demographics form, standardized testing (including cognitive testing with the Wechsler Abbreviated Scale of Intelligence [WASI]; Wechsler, 1999), and self-report questionnaires (including the AQ and the Behavior Assessment System for Children, Second Edition [BASC-2] Self Report of Personality – College Age [Reynolds & Kamphaus, 2004]). They also ran through a mock scan procedure to ensure that they would be able to remain still for the real MRI scans.

All MRI scans occurred during the second visit at the Georgia State University/Georgia Institute of Technology Joint Center for Advanced Brain Imaging. Participants completed a metal screening form and reviewed this form with a trained MRI technologist. The T1-weighted images and DTI scan were collected as part of a longer scanning procedure that took

approximately one hour to complete. Participants also completed functional MRI (fMRI) runs as part of the larger study protocol. The fMRI data were not included in this study; however, we note the fMRI procedure to provide the full context for the data collection. Due to the loud sounds produced by the MRI scanner, participants wore earplugs and headphones during all scans. During three fMRI runs, participants completed the scanner version of the DISC task (Robins et al., in prep). After the scan, participants completed the behavioral administration of the DISC task. This took approximately 20 to 30 minutes to complete. For the behavioral DISC task, the two runs were counterbalanced. Participants enrolled through the GSU participant pool received one hour of course credit for each hour of participation. Participants who completed all testing and scanning procedures received $50 compensation for time and travel expenses (in addition to course credit for those enrolled through the GSU participant pool).

2.4 ANALYSES

2.4.1 Specific Aim 1: Mentalizing and Autism Traits

The first aim of this project was to examine the relationship between self-reported levels of autism traits and mentalizing abilities. To address this aim, we reviewed descriptive statistics for the main variables of our project and evaluated whether score distributions met assumptions of normality by checking values of skewness and kurtosis. We converted values of skewness and kurtosis to z-scores to determine whether score distributions violated assumptions of normality. We also examined the distributions of scores for outliers. Some score distributions did not meet assumptions of normality. Therefore, we used non-parametric Kendall's tau correlation coefficients to examine relationships among main variables. We considered a statistical relationship significant if its associated p-value was at or less than .05.

2.4.2   Specific Aims 2 and 3: Autism Traits, Mentalizing, and FA Values

The second and third aims of this project were to evaluate whether self-reported autism

traits and mentalizing abilities predict FA values in bilateral UF and ILF, respectively. We used

bilateral corticospinal tract (CST) as a control tract to test the specificity of the results for UF and

ILF. Using TBSS, we projected each participant's aligned FA data onto the FA skeleton. We

created one mask of bilateral UF, ILF, and CST from the skeletonized FA maps using the Johns

Hopkins University (JHU) White-Matter Tractography Atlas (Hua et al., 2008). The purpose of

this mask was twofold: this mask limits our analyses to our tracts of interest and ensures that the

analyses for our experimental and control conditions, the UF and ILF versus the CST,

respectively, are directly compared in the same statistical test (see Nieuwenhuis, Forstmann, &

Wagenmakers, 2011 for discussion and Hecht, E. E. et al., 2014 for example). Using the General

Linear Model (GLM) tool in FSL, we built a design to model whether five separate explanatory

variables (EVs) accounted for variations in FA values in tracts of interest across participants. The

five EVs were age, AQ total score, DISC Mentalizing score, WASI Full Scale Intelligence

Quotient (FSIQ), and BASC-2 Somatization score. All EVs were mean-centered. We included

FSIQ in the model because previous research has demonstrated that measures of general

intelligence are related to multiple measures of white matter microstructure (e.g., Penke et al.,

2012). The BASC-2 Somatization score served as a control variable in our model. We set up

contrasts to test positive and negative effects of each EV while taking into account the effects of

all other EVs in the model. Next, we used this design to run Randomise in FSL. Randomise uses

Monte Carlo permutation tests and nonparametric inferences for voxelwise cross-participant

statistics (Nichols & Holmes, 2001; Winkler, Ridgway, Webster, Smith, & Nichols, 2014). We

ran this analysis using 5,000 permutations using the Threshold-Free Cluster Enhancement

(TFCE) option for 2D TBSS data. To check for significant voxels, we set the threshold for the FWE-corrected (i.e., family-wise error rate is controlled) p-value images for each contrast at 0.95. It is important to note that images are saved as $1 - p$, so setting the threshold at 0.95 corresponds to a p-value of .05. We used the JHU White-Matter Tractography Atlas (Hua et al., 2008) to identify the location of significant clusters.

As a secondary confirmation of the tracts that pass through the significant cluster, we decided to conduct tractography for each of the 24 participants using the significant cluster as a seed point. This procedure allowed us to visually inspect the tracts that passed through this cluster for each participant. First, we ran tbss_deproject to transform the significant voxels on the FA skeleton back to native space for each participant. Then we generated a mask for each participant of the significant voxels in native space. We used each mask as a seed point from which to run probabilistic tractography for each of the 24 participants. We conducted probabilistic tractography using PROBTRACKX in FDT (Behrens et al., 2003; Behrens, Berg, Jbabdi, & Woolrich, 2007). We set the curvature threshold to 0.2, the step length to 0.5mm, and the number of samples to 5000. For an overview of the processing steps for tractography with all parameters, please see the script in Appendix B. We then set a threshold for each participant's tractography results at 1% of the total number of fibers. We registered the resulting tract images to MNI space and created a binary image of the tracts using fslmaths. We created a composite image of the tracts from all 24 participants and then set the threshold to show tracts with above-threshold connectivity for 50% of participants. We visually inspected the tracts using the MRI Atlas of Human White Matter (Mori et al., 2005). Additionally, we calculated the average FA value in significant clusters for each participant by creating binary masks of the significant voxels in native space and multiplying each participant's mask by his/her FA image.

3   RESULTS

3.1   DESCRIPTIVE STATISTICS

Descriptive statistics for variables of interest for the total sample are shown below (see Table 1). In our sample, the average AQ total score was 15.46 (SD = 4.96) and the range was 9 to 29. This score range was similar to the AQ total score range (9 to 34) in the neurotypical sample in the study by Iidaka and colleagues (2012). The average DISC Mentalizing score across participants was 1.84 (SD = 0.57) and the range was 0.46 to 3.29. Histograms for AQ total scores and average DISC Mentalizing scores are shown in Figures 3.1 and 3.2, respectively.

Table 3.1 Means, Standard Deviations, Medians, and Range for Main Variables

Variable	M (SD)	Median	Range
Age in Years	21.92 (1.79)	21.95	18.37 – 25.58
DISC Mentalizing Score	1.84 (.57)	1.76	0.46 – 3.29
AQ Total Score	15.46 (4.96)	14.00	9 – 29
EQ Total Score	49.83 (10.48)	50.50	29 – 67
WASI			
FSIQ	109.21 (10.19)	110.00	92 – 129
Vocabulary	54.50 (8.04)	55.50	38 – 69
Matrix Reasoning	56.17 (5.69)	57.00	46 – 65
BASC-2			
Atypicality	45.79 (6.33)	42.00	42 – 67
Locus of Control	43.75 (6.58)	42.00	39 – 68
Social Stress	43.21 (8.64)	40.50	34 – 60
Anxiety	45.25 (8.21)	46.00	30 – 63
Depression	44.25 (3.73)	44.00	40 – 55
Sense of Inadequacy	44.08 (7.78)	42.00	35 – 69
Somatization	46.96 (7.79)	44.00	41 – 69
Attention Problems	46.67 (9.65)	45.00	33 – 65
Hyperactivity	44.71 (8.06)	43.00	33 - 67
Sensation Seeking	48.58 (11.00)	46.00	34 – 72
Alcohol Abuse	46.92 (5.71)	44.00	43 – 66
School Maladjustment*	44.61 (9.72)	41.00	34 – 74
Relations with Parents^	51.21 (10.57)	54.00	25 – 62
Interpersonal Relations^	56.21 (6.70)	57.00	41 – 65
Self-Esteem^	54.13 (7.69)	56.00	38 – 63
Self-Reliance^	56.04 (7.26)	56.00	41 - 69

Note. 1. AQ = Autism Spectrum Quotient. Scores are presented as raw scores. Scores equal to or greater than 32 indicate levels of autism traits consistent with levels reported by individuals with ASD. 2. EQ = Empathy Quotient. Scores are presented as raw scores. Scores equal to or less than 30 indicate levels of empathy consistent with levels reported by individuals with ASD. 3. FSIQ = Full Scale IQ. WASI FSIQ presented as a standard score, and WASI Vocabulary and Matrix Reasoning scores presented as T-scores. 4. All BASC-2 scores presented as T-scores. ^ = Adaptive scales. For Clinical scales, scores between 60-69 are At-Risk and scores ≥ 70 are Clinically Significant. For Adaptive scales, scores between 31-40 are At-Risk and scores ≤ 30 are Clinically Significant. 5. DISC Mentalizing Score presented as a raw score.
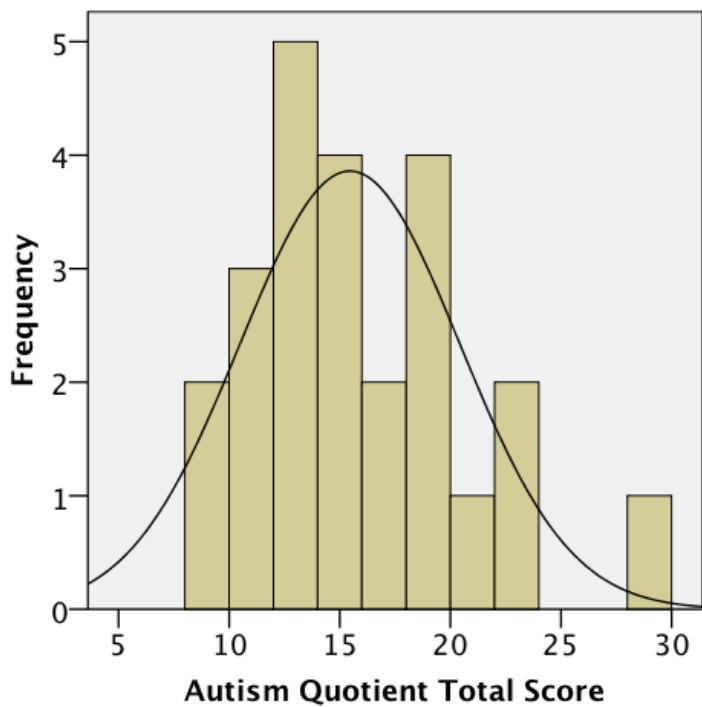 *Based on 23 participants

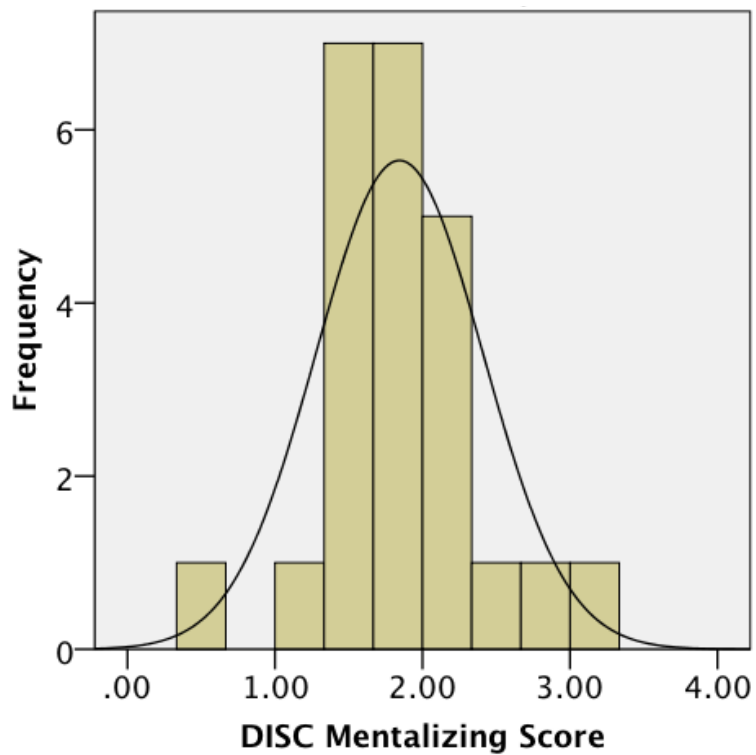Figure 3.1 Histogram of Autism Quotient (AQ) Total Scores

Figure 3.2 Histogram of DISC Mentalizing Scores

AQ total score and BASC-2 Somatization score distributions were significantly positively

skewed and DISC Mentalizing score and BASC-2 Somatization score distributions had

significant positive kurtosis values (see Table 2). Our analytic procedures do not require score

distributions to be normal. However, we attempted to use logarithm (log10) and square root

transformations to bring our data to a normal distribution for the use of parametric statistics

(Field, 2009). Both transformations eliminated the significant positive skew for AQ total score

but did not eliminate the significant positive skew and kurtosis values for BASC-2 Somatization

scores or the significant positive kurtosis value for DISC Mentalizing score. We ran our analyses

twice, first using untransformed data and then using transformed (log10) data. Results of the two

sets of analyses were not appreciably different, therefore we report results for the untransformed

data unless otherwise noted.

Table 3.2 Skewness and Kurtosis Values, Standard Errors, and Associated Z-scores

	Entire Sample (n=24)					
Variable	Skewness Value	SE Skewness	Z-score Skewness	Kurtosis Value	SE Kurtosis	Z-score Kurtosis
DISC Mentalizing Score	0.40	0.47	0.84	1.96	0.92	2.14*
AQ Total Score	0.93	0.47	1.97*	0.86	0.92	0.94
WASI FSIQ	-0.11	0.47	-0.23	-0.69	0.92	-0.75
BASC-2 Somatization Score	2.06	0.47	4.36***	4.02	0.92	4.38***
EQ Score	-0.17	0.47	-0.36	-1.00	0.92	-1.08

Note. FSIQ = Full Scale IQ; AQ = Autism Spectrum Quotient; EQ = Empathy Quotient; *p<.05; ** p< .01; ***p<.001

We also examined our score distributions for outliers. Aguinis, Gottfredson, & Joo (2013) recently reviewed the complexities of outliers and how they are handled in research, and they cautioned researchers from treating all outliers as "problematic observations that somehow must be 'fixed'" (p. 280). With this is mind, we first examined our data for "statistical" outliers by visually inspecting boxplots for AQ total score, DISC Mentalizing score, BASC-2 Somatization score, WASI FSIQ, EQ total score, and age. Next, we examined the scores that appeared beyond the tails of the boxplots and evaluated whether these scores were meaningful in our sample or errors. We decided to identify scores as outliers if they were above clinical cutoffs for impairment. We identified two DISC Mentalizing scores, one high score and one low score, by visual inspection. Since the DISC Mentalizing score does not have an established cutoff point for impairment, we considered both scores to be meaningful data points. We also identified two BASC-2 Somatization scores and one AQ total score, all high scores, by visual inspection. We determined that the two BASC-2 Somatization scores were below the "Clinically Significant" threshold for the BASC-2 (i.e., T-scores at or above 70) and that the one AQ total score was also below the clinical cut-off for the AQ (i.e., total score of 32 or higher). Thus, all of our data points appear to be meaningful and represent the range of abilities and qualities measured in our neurotypical sample.

3.2   SPECIFIC AIM 1: MENTALIZING AND AUTISM TRAITS

Hypothesis 1a: *Higher levels of self-reported autism traits would be associated with lower levels of mentalizing.* Kendall's tau correlation coefficients among the main variables of interest are shown in Table 3. In contrast to our hypothesis, AQ total scores were not significantly related to DISC Mentalizing scores ($\tau = .01$, $p = .94$). AQ total scores were negatively associated with EQ total scores ($\tau = -.39$, $p = .01$).

Table 3.3 Kendall's Tau Correlation Coefficients Among Main Variables

Variable	1	2	3	4	5	6	7
1. Age	1.00	-	-	-	-	-	-
2. Sex	-.02	1.00	-	-	-	-	-
3. WASI FSIQ	.09	.05	1.00	-	-	-	-
4. DISC Mentalizing Score	-.004	.34	-.11	1.00	-	-	-
5. AQ Total Score	.15	.12	-.08	.01	1.00	-	-
6. BASC-2 Somatization	.05	-.30	.008	-.16	.07	1.00	-
7. EQ Total Score	-.07	-.17	.05	-.06	-.39**	-.06	1.00

Note. FSIQ = Full Scale IQ; AQ = Autism Spectrum Quotient; EQ = Empathy Quotient; ** *p*=.01

3.3   SPECIFIC AIM 2: AUTISM TRAITS AND FA VALUES

Hypothesis 2a: Higher levels of autism traits would be associated with lower FA values in the UF. For the positive and negative contrasts of AQ total score, no significant voxels survived correction for multiple comparisons in bilateral UF.

Hypothesis 2b: Higher levels of autism traits would be associated with lower FA values in the ILF. A cluster of voxels in the left hemisphere for the positive contrast for AQ total score survived correction for multiple comparisons. This cluster contained 101 voxels and the volume was 101mm. The center of the cluster was located at MNI coordinates X=129, Y=93, Z=73 (see Figure 3.3). In the JHU White-Matter Tractography Atlas, this location has a 37% probability for ILF, a 21% probability for inferior fronto-occiptal fasciculus, a 3% probability for superior longitudinal fasciculus (temporal part), and a 3% probability for superior longitudinal fasciculus. From our visual inspection of the probabilistic tractography results, we determined that the tracts that pass through this cluster match the known trajectory of left ILF (see Figure 3.4). This indicates that higher levels of self-reported autism traits are associated with higher FA values in a region of left ILF.
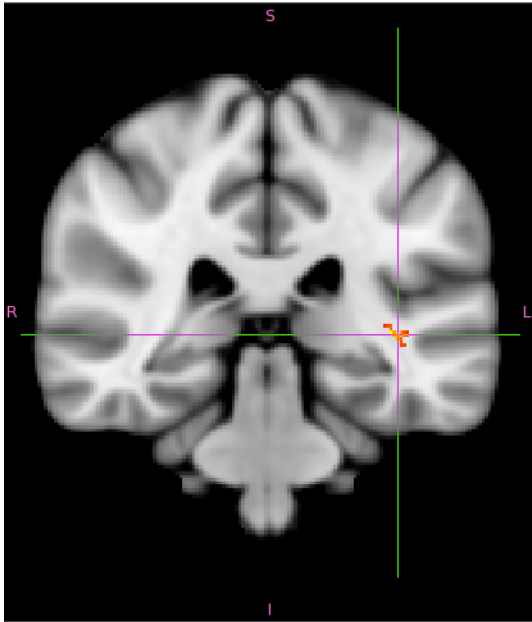
Figure 3.3 Coronal View of Voxels with Significant Positive Association with FA Values and AQ Total Scores in Left ILF
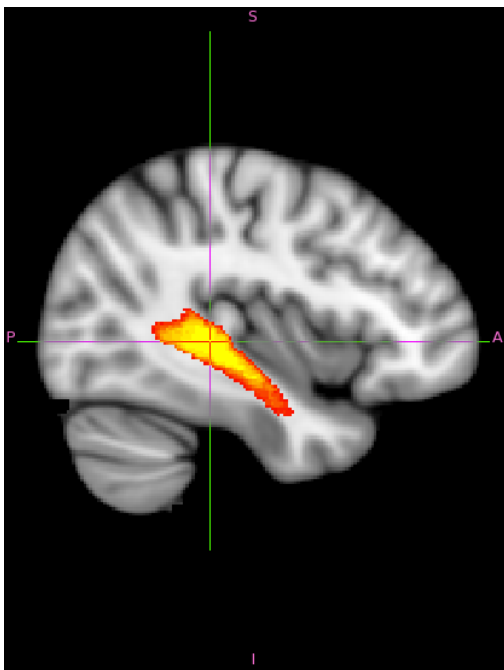
Figure 3.4 Composite Image of Probabilistic Tractography Results for Entire Sample
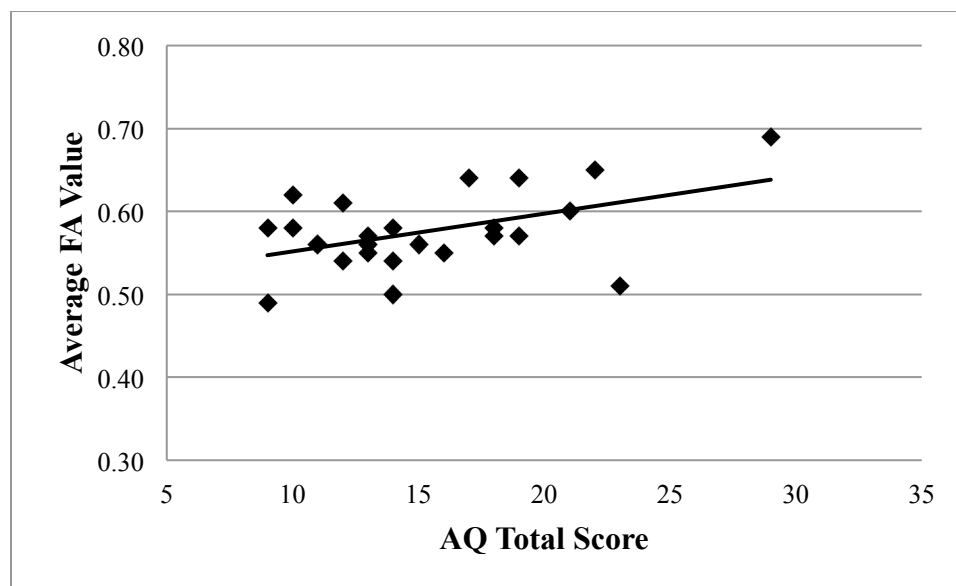
Figure 3.5 Average FA Value in Left ILF Cluster by AQ Total Score

Figure 3.5 shows a scatterplot that illustrates the positive relationship of average FA

values in the significant cluster with AQ total scores. We calculated a Pearson's product-moment

correlation coefficient using logarithm transformed AQ total scores and average FA values in the

significant cluster and found a significant positive relationship (r (22) = .42, p = .04).

Hypothesis 2c: Levels of autism traits would not be associated with FA values in the CST.

For the positive and negative contrasts of the AQ total score, no significant voxels survived

correction for multiple comparisons in bilateral CST.

3.4   MENTALIZING AND FA VALUES

Hypothesis 3a: Poorer performance on a mentalizing task would be associated with

lower FA values in the UF. For the positive and negative contrasts of the DISC Mentalizing

score, no significant voxels survived correction for multiple comparisons in bilateral UF.

Hypothesis 3b: Poorer performance on a mentalizing task would be associated with lower FA values in the ILF. For the positive and negative contrasts of the DISC Mentalizing score, no significant voxels survived correction for multiple comparisons in bilateral ILF.

Hypothesis 3c: Performance on a mentalizing task would not be associated with FA values in the CST. For the positive and negative contrasts of the DISC Mentalizing score, no significant voxels survived correction for multiple comparisons in bilateral CST.

3.5   EXAMINATION OF DISC MENTALIZING SCORE

As previously discussed, we created a composite score called "DISC Mentalizing score" that corresponds to the average AI score for Social DISC across FRIENDS and SIZE cues; this composite score served as our overall measure of mentalizing. In order to gain a better understanding of the implications of this decision, we examined the average AI scores for each combination of the type of clip (i.e., Social DISC and Random DISC) and the cue shown before the movie (i.e., FRIENDS, SIZE, or WATCH). We had three different movie type/cue combinations: Social DISC FRIENDS cue, Social DISC SIZE cue, and Random DISC WATCH cue. We ran a univariate analysis of variance to examine differences among these three combinations with average AI scores (across participants) as the dependent variable. We found a significant effect of movie type/cue on average AI score $F(2, 15) = 25.90, p < .001$, partial $\eta^2 = .78$. Post hoc comparisons using Bonferroni correction indicated that the average AI score for Social DISC FRIENDS cue ($M = 2.18, SD = .24$) was significantly higher than the average AI score for Social DISC SIZE cue ($M = 1.51, SD = .45$), and this score (Social DISC SIZE cue) was significantly higher than the average AI score for Random DISC WATCH cue ($M = .69, SD = .17$), all $p < .01$. We also used non-parametric Kendall's tau correlation coefficients to examine

relationships among participants' average AI scores among these three movie type/cue combinations. There were no significant relationships among the three combinations, all $p < .05$.

Since the Social DISC FRIENDS cue average AI scores were significantly higher than the average AI scores other two movie type/cue combinations, we decided to check whether the average AI scores for the Social DISC FRIENDS cue had different relationships with AQ total scores and EQ total scores. We used logarithm (log10) transformations so that the score distributions all met the assumption of normality. We ran Pearson product-moment correlations among average AI scores for the Social DISC FRIENDS cue, AQ total scores, and EQ total scores. None of the correlation coefficients were significant, all $p > .05$. Based on this result, we determined that combining the average AI scores for the Social DISC FRIENDS cue and the Social DISC SIZE cue was appropriate.

3.6   SECONDARY ANALYSES

AQ Subscales and FA Values. To explore the significant positive relationship between AQ total score and FA value in left ILF, we decided to examine the potential unique effects of the AQ subscale scores on FA values in our tracts of interest. The five subscales do not share any items. We designed a model using GLM in FSL to test whether one or more of the AQ subscale scores were associated with FA values. We set up positive and negative contrasts for Social Skill, Attention Switching, Attention to Detail, Communication, and Imagination. Next, we used this design to run Randomise in FSL. We ran this analysis using 5,000 permutations using the Threshold-Free Cluster Enhancement (TFCE) option for 2D TBSS data. To check for significant voxels, we set the threshold for the FWE-corrected (i.e., family-wise error rate is controlled) p-value images for each contrast at 0.95. Images are saved as 1-p, so the threshold of 0.95 corresponds to a p-value of .05. No contrasts survived correction for multiple comparisons.

Removal of High AQ Total Score. Iidaka and colleagues (2012) found that their

significant result of a positive relationship between AQ total score and volume of connectivity in

left ILF vanished when they removed two participants who exceeded the clinical cutoff for the

AQ total score. Although our sample does not have any participants who exceed the clinical

cutoff for the AQ, we decided to run our analyses with and without one participant who received

the highest AQ total score (29) that was +2.24 standard deviation units above the average AQ

total score in our sample. Removing this participant did not appreciably change the correlation

coefficient results. However, the results of our DTI analysis changed, such that we no longer

found a significant positive association between AQ total score and FA values in left ILF (i.e.,

for the positive AQ total score contrast, no significant voxels survived correction for multiple

comparisons in left ILF).

4   DISCUSSION

In order to gain a better understanding of the neural underpinnings of social cognition,

the current study examined mentalizing abilities, self-reported autism traits, and white matter

microstructure in UF and ILF. We focused our analyses to UF and ILF because these tracts

connect grey matter regions implicated in a mentalizing network proposed by Abu-Akel and

Shamay-Tsoory (2011).

Contrary to our first hypothesis, mentalizing abilities were not related to self-reported

autism traits. This result was unexpected because mentalizing abilities are considered by some

researchers to underlie some of the core deficits of ASD (Baron-Cohen, Leslie, & Frith, 1985;

Tager-Flusberg, 2007) and individuals with ASD often demonstrate deficits in cognitive and

affective mentalizing (e.g., Brent, Rios, Happé, & Charman, 2004; Klin, 2000). We interpret the

lack of association to be an artifact of our measure of mentalizing abilities rather than indicative of the relationship between mentalizing and autism traits.

To measure mentalizing abilities, we used a new task, the DISC task, developed by our research team. We modeled the DISC task after the Social Attribution Task (SAT) by Klin (2000) and used one of the same indices, the Animacy Index (AI), to code responses on the DISC task. Scores on the AI range from 0-6, with higher scores indicating greater complexity of social attributions. Although the DISC task is based on a paradigm that has successfully elicited mentalizing (e.g., Klin, 2000), our version of the task differs substantially from the SAT. These differences and their potential impact on our findings are discussed below.

We designed the DISC task to be appropriate for both behavioral and fMRI studies (Robins et al., in prep). Thus, we developed 14 unique video clips of three geometric shapes that appear to interact with one another in a social manner. Each clip lasts 10 seconds, and none of our clips are explicitly related to clips seen before and after one another. In contrast, the SAT consists of one video of three geometric shapes interacting together that lasts for 50 seconds. The longer duration of the video allows for the social interactions among the shapes to be more complex. In the SAT, participants provide narratives of "what happened" in the video after watching the 50-second clip *twice*, and then provide six additional narratives to six segments of the same 50-second clip.

Klin (2000) reported that the average score on the AI in a sample of 20 control individuals similar in age to our sample was 3.5 (SD = 1.4) for the SAT. In our sample of 24 neurotypical individuals, the average score on the AI (called the DISC Mentalizing score for clarity throughout this paper) was 1.84 (SD = .57) for the DISC task. Given that the clips of the SAT are interconnected and depict a much longer social interaction than the clips of the DISC

task, it is not surprising that the AI scores are much lower for the DISC task than the SAT. The fact that participants watched the 50-second clip twice before providing their first narratives may have also allowed them to conceptualize a longer, richer narrative of the interaction of the shapes. The AI measures the overall *complexity* of social attribution. The shorter duration of the DISC task videos limits the complexity of the social interactions and thus restricts the range of the complexity of mental state attributions produced by individuals.

The results for our third set of hypotheses are intricately tied to the prior discussion of the DISC task. We expected to find that lower DISC Mentalizing scores would be related to lower FA values in UF and ILF given that these tracts connect regions implicated in the proposed mentalizing network by Abu-Akel and Shamay-Tsoory (2011). Contrary to expectations, we did not find any associations among mentalizing abilities and FA values in these white matter pathways. Given the limitations of the DISC Mentalizing scores, we interpret this lack of relationship to be more representative of measurement artifact rather than a true lack of association.

We found partial support for our second set of hypotheses. We expected that higher levels of self-reported autism traits would be negatively associated with FA values in UF and ILF. Our results showed that self-reported autism traits were only related to FA values in left ILF, and the direction of this relationship was opposite to our hypothesis. As levels of self-reported autism traits increased, so too did FA values in a region of left ILF. This finding concurs with results from Iidaka and colleagues (2012). The authors examined autism traits in a neurotypical sample and found that a higher volume of connectivity of left ILF positively correlated with self-reported autism traits. Although we expected to find a negative relationship between white matter in ILF and autism traits given that we used a different measure of white

matter microstructure from Iidaka and colleagues (i.e., FA values vs. volume of connectivity) and given that multiple studies have identified lower FA values in individuals with ASD (e.g., Koldewyn et al., 2014), our results support the robustness of a positive association between FA values in left ILF and self-reported autism traits in neurotypical adults.

Similar to Iidaka and colleagues (2012), in our sample the significant positive relationship between AQ total score and FA values in left ILF became non-significant after we removed the participant with the highest AQ total score. This suggests that the results changed due to a loss of range of autism traits measured in our sample. Although many studies of ASD examine differences between categorical groups (i.e., individuals with ASD vs. neurotypical individuals), another useful approach may be to measure autism traits continuously in individuals with and without a clinical diagnosis of ASD. Multiple studies have examined autism traits in non-clinical samples; however, it is common for the analyses to create "low" and "high" groups of autism traits. For example, Jameel, Vyas, Bellesi, Roberts, and Channon (2014) measured autism traits in full-time university students using the AQ, created "low AQ" and "high AQ" groups, and compared responses of the groups on a novel pro-social behavior task. The authors reported differences between the two groups and suggested that the trait-based approach to studying ASD may be useful understanding intact and disrupted social functioning. Given that autism traits seem to be distributed continuously in the general population (Constantino & Todd, 2003; Robinson et al., 2011) and that some of the neurobiological correlates of ASD appear to represent disruptions in neural networks associated with social cognition in neurotypical individuals (e.g., Kana et al., 2014; Lombardo et al., 2011), combining individuals with and without ASD into one sample for analyses may allow for an examination of the full range of autism traits and their associated behavioral, cognitive, and neurobiological correlates.

Previous studies have found reduced FA values in right (e.g., Jou et al., 2011; Kana et al., 2014; Koldewyn et al., 2014) and left (e.g., Jou et al., 2011) ILF in individuals with ASD compared to individuals in control groups. The positive relationship between left ILF FA values and self-reported autism traits in our neurotypical participants supports the involvement of the ILF in the expression of autism traits in clinical and non-clinical samples. Altered microstructure of ILF may result in the expression of autism traits because this associative white matter bundle connects multiple brain regions implicated in social cognition, including superior temporal sulcus, fusiform face area, and amygdala (Jou et al., 2011; Abu-Akel & Shamay-Tsoory, 2011).

We did not find a significant relationship between FA values in right ILF and self-reported autism traits; this suggests that lateralization effects may be important for understanding the role of ILF in mentalizing. Research findings on lateralization effects in social cognition is mixed, and this is complicated further by the fact that microstructural differences in both left and right ILF have been found in individuals with ASD in different studies. In studies that examine damage to the right and left hemispheres, the right hemisphere is often identified as being especially important for social cognition. For example, Yeh and Tsai (2014) reported that individuals who suffered right stroke or left stroke demonstrated poorer performance on verbal and non-verbal tasks of cognitive and affective mentalizing compared to control individuals. Notably, individuals who experienced right stroke showed poorer performance on the nonverbal task of cognitive mentalizing compared to individuals who experienced left stroke. However, it is clear that social cognitive functions are not confined to the right hemisphere. Siedel and colleagues (2010) examined the neurobiological correlates of causal attribution (i.e., internal attribution vs. external attribution) in social cognition. The authors found that internal attributions (i.e., self-caused) activated brain regions in the right hemisphere, including TPJ,

right superior temporal gyrus, and right supermarginal gyrus. In contrast, external attributions (i.e., other person or situation-caused) activated a left lateralized fronto-temporoparietal network that included left TPJ, left superior, middle, and superior medial frontal gyrus, and bilateral precuneus. The role of differentiating the self from others is an integral component of mentalizing (Abu-Akel & Shamay-Tsoory, 2011) and may be required to varying degrees in different mentalizing tasks. Our mentalizing task depended heavily on making external attributions to geometric shapes based on specific perceptual cues, and this may account for our significant finding in the left hemisphere.

Our results and those of previous studies examining FA values highlight a key issue in structural connectivity studies: the need for a more comprehensive understanding of the relationship among measures of white matter microstructure and function. Although early DTI studies equated higher FA values with greater white matter "integrity," the current view of FA values is more specific (Jones, Knösche, & Turner, 2013). Jones and colleagues (2013) highlight that scalar measures derived from the diffusion tensor, such as FA values, indicate that "some orientation dependent aspects of the microstructure of the tissue are different" (p. 250) and that further interpretation of FA values, particularly at a biophysical level, must be completed with strong theoretical backing or data from other sources. Thus, from our data we can conclude that microstructural differences in the left ILF influence the expression of autism traits in neurotypical adults. Our finding that self-reported autism traits were not related to FA values in bilateral CST provides greater confidence in the specificity of the relationship between self-reported autism traits and ILF. However, we cannot explicitly identify the microstructural differences in left ILF that drive this relationship with the current data.

Although multiple studies have found aberrant connectivity in UF in individuals with ASD, we did not find a significant relationship between FA values in UF and self-reported autism traits in neurotypical adults. This may indicate that aberrant FA values in UF are associated with clinically significant autism traits rather than sub-clinical autism traits. Von Der Heide and colleagues (2013) suggested that UF might play an important role in allowing information regarding the environment (including individuals) and associations with that information (e.g., emotional responses) to modify behavior. Disruptions in UF may lead to greater behavioral expressions associated with ASD given the proposed role of UF in facilitating decision making related to social cognition.

Our method of analyzing the DTI data played an integral role in the results we found. TBSS is considered a conservative approach to examining white matter because it limits analyses to voxels containing peak values of FA that correspond to the "center" of white matter tracts among participants (Smith et al., 2006). The benefits of this approach include a reduction in partial volume effects (i.e., we have greater certainty that the voxels contain predominantly white matter rather than other tissue types) and greater confidence that we are examining regions of tracts shared among all participants. However, TBSS does not examine potential differences among the total volume of white matter tracts (including regions beyond the center of the tracts), the trajectory of tracts, or the average FA value along entire tracts (rather than a voxel-wise approach). Thus, it is possible that our results may have been different had we selected a different methodological approach for examining FA values. Relatedly, FA values in a given voxel are affected by multiple biophysical properties that we did not directly measure, including the packing density of fibers, the degree of myelination of fibers, and the orientation of fibers (Beaulieu, 2002). For example, FA values are generally lower in voxels that contain multiple

crossing or "kissing" fibers (Oouchi, et al., 2007; Jones et al., 2013). UF is a tract identified as being susceptible to effects of "kissing" fibers (Danielian, Iwata, Thomasson, & Floeter, 2010), and consequently our measurement of FA values in UF may be impacted differentially by this factor.

This study has a number of limitations. One limitation that we have already mentioned is the use of the DISC task with the AI to measure mentalizing abilities. The short duration of the clips in the DISC task limited the complexity of the social interactions depicted in the clips and consequently restricted the range of AI scores. We may have found greater support for the relationships among mentalizing abilities, autism traits, and white matter tracts if our measure of mentalizing had elicited a greater range of scores. Another limitation of our study is that we did not include a second measure of mentalizing. The DISC task is a relatively new task. Although the DISC task elicits activation in brain regions implicated in the mentalizing network, including bilateral superior temporal gyrus, medial prefrontal cortex, and right amygdala (Robins et al., in prep), performance on the DISC task has not been directly compared to performance on other validated mentalizing tasks. Including such measures would have increased our confidence in the construct validity of the DISC task. Finally, another potential limitation of this study is that we had a relatively high percentage (62.5%) of women in this study. ASD is almost five times as common among males than females (CDC, 2014). Many studies that examine neurobiological correlates of ASD utilize samples of individuals with and without ASD that have greater proportions of males than females. This difference may limit the comparability of our findings with such studies.

Our study represents an attempt to illuminate relationships among social cognitive abilities and the neural networks that underlie their behavioral expressions. Our approach is in

line with conceptualizations of behaviors and abilities as arising from coordinated activity of

cortical and subcortical brain regions rather than from activity in a single brain region (Bassett &

Gazzaniga, 2011; Bullmore et al., 2009; Koziol & Budding, 2009). We have several ideas of how

to build upon this study in future work. First, we may want to develop a social attribution coding

scheme specific to the DISC task. Similar to the AI, such a coding scheme might give more

weight to specific forms of mental state attributions (e.g., affective statement, goal-oriented

statement) than to other forms of social attributions (e.g., identifying a shape as an animate agent

of action). However, a DISC-specific coding scheme would not focus on the overall complexity

of the social attributions for each clip. Second, future work should examine multiple measures of

white matter microstructure when trying to elucidate neural networks. Different measures of

white matter microstructure provide unique and complementary information on the biophysical

properties of white matter bundles (Soares et al., 2013), and such information will be useful for

interpreting the biological differences associated with behavioral measures. Finally, future

studies should examine relationships among social cognitive abilities and neural networks in

clinical and nonclinical samples. We are currently using the study procedures described in this

paper to collect data from adults with ASD. This will allow us to examine whether we find the

same relationships among clinically significant autism traits and white matter. Although we

focused our project on autism traits, numerous other neurodevelopmental and neurodegenerative

disorders involve disruptions in social cognitive abilities. Abu-Akel and Shamary-Tsoory (2011)

suggest that their model of the neural network for cognitive and affective mentalizing may be

useful for identifying specific biological changes within that same network that lead to different

patterns of social cognitive impairment in clinical conditions. This transdiagnostic approach is

useful for developing a fuller understanding of the complex cognitive and neurobiological

processes that underlie social cognition.

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APPENDICES

4.1   APPENDIX A

Animation Index (AI) Coding System (Adapted from Klin, 2000)

Behaviors

A   Behaviors that necessitate actors or agents, but which are not uniquely or necessarily human behaviors, nor do they necessarily require any attribution of mental or feeling states (e.g., chasing, fighting, destroying)

B   Verbs or behaviors that do not involve an explicit mental state but are uniquely human (e.g., talking, says, or a quotation)

C   Behaviors that are uniquely human by virtue of implied indication of a shared mental state without which the behavior cannot occur (e.g., celebrating, trapping, hiding)

D   Behaviors that are uniquely human by virtue of direct indication of an awareness by one character of another's mental state, accompanied by an attempt to alter the second character's mental state (e.g., intimidation, trickery, taunting, bullying)

Perceptions

E   Sensory experiences or attention which are not uniquely human (e.g., look, watch, notice)

Emotions

F   Emotional terms that usually result from a behavior or an action, but which do not necessarily result from a social action, or which are not uniquely human (e.g., happy, sad, scared, mad, alarmed, panicked)

G   Emotional terms which result only from a social situation (e.g., envious, sulking, bitter, mended his ways, expressing sour grapes, admiration)

Cognition, Intention, Motivation

H   Lower developmental level: mental state terms expressing desire or knowledge (e.g., want to, know, mistake)

I   Higher developmental level: mental state terms expressing beliefs, thoughts, imagination, plans (e.g., pretending, remembering, decision)

Relationships or Personality Traits

J   Allusion to a person as constrained by his or her features (e.g., big guy, little guy, kid)

K   Allusion to a person as constrained by his or her relationship to another (e.g., is a daddy, mommy, or baby)

L   Allusion to a person as constrained by his or her actions or attribution of personality traits (e.g., to be a bully, friends, companions, curious, timid, shy)

Symbolic Nature

M   An acknowledgment of the symbolic nature of an object or shape (e.g., represents, stands for, symbolizes, a home, domain)

Score	Criteria
0	No human agency; mechanistic, geometric reasoning only
1	A or E or J
2	B or C or F or H or K or M
3	D or G or I or L
4	At least two of D or G or I or L, but not two of the same category
5	At least three of D or G or I or L, but not two of the same category
6	Four of D or G or I or L, but at least one of each

4.2   APPENDIX B

<div align="center">Script for DTI processing pipeline</div>

```perl
#!/usr/bin/perl

$WORKINGDATAPATH = "/home/lbradstreet1/workingdata/";
$SOURCEDATAPATH = "/home/lbradstreet1/robins_dcm/";

$subjSTRING="001 002 003 004 005 006 007 008 010 011 012 013 014 015 016 017 018 019
020 021 022 023 024 025"; #
@subj = split(/ /,$subjSTRING);

#################
#### Convert DICOMs, set up directories for analysis
#################


for($k=0;$k<=$#subj;$k++)  {

print "#\$ -cwd\n";
print "#\$ -S /bin/bash \n";
print "export FSLDIR=/usr/local/fsl  \n";
print ". /usr/local/fsl/etc/fslconf/fsl.sh \n";
print  "export PATH=\$PATH:\$FSLDIR/bin \n";
print "#!/bin/bash \n";


$statement  = "mkdir $WORKINGDATAPATH/sub" . $subj[$k] . " ";
#print "$statement \n";

$statement  = " dcm2nii -o $WORKINGDATAPATH/sub" . $subj[$k] . "/ ";
$statement .= " /home/lbradstreet1/robins_dcm/RobinsfMRI/PD*_" . $subj[$k] . "_*/ep*/* ";
#print "$statement \n";

$statement  = " mv $WORKINGDATAPATH/sub" . $subj[$k] . "/*.nii.gz
$WORKINGDATAPATH/sub" . $subj[$k] . "/data.nii.gz ";
#print "$statement \n";

$statement  = " mv $WORKINGDATAPATH/sub" . $subj[$k] . "/*.bval
$WORKINGDATAPATH/sub" . $subj[$k] . "/bval ";
#print "$statement \n";

$statement  = " mv $WORKINGDATAPATH/sub" . $subj[$k] . "/*.bvec
$WORKINGDATAPATH/sub" . $subj[$k] . "/bvec ";
#print "$statement \n";
```

```
$statement = " mv $WORKINGDATAPATH/sub" . $subj[$k] . "/data.nii.gz
$WORKINGDATAPATH/sub" . $subj[$k] . "/data_raw.nii.gz ";
#print "$statement \n";

$statement = " mkdir $WORKINGDATAPATH/sub" . $subj[$k] . "/test ";
#print "$statement \n";

$statement = " cp $WORKINGDATAPATH/sub" . $subj[$k] . "/data_raw.nii.gz
$WORKINGDATAPATH/sub" . $subj[$k] . "/test/ ";
#print "$statement \n";

$statement = " fslsplit $WORKINGDATAPATH/sub" . $subj[$k] . "/test/data_raw.nii.gz
$WORKINGDATAPATH/sub" . $subj[$k] . "/test/data_test -t ";
#print "$statement \n";

$statement = " fslmaths $WORKINGDATAPATH/sub" . $subj[$k] . "/test/data_test0000.nii.gz
-add $WORKINGDATAPATH/sub" . $subj[$k] . "/test/data_test0031.nii.gz -div 2
$WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0 ";
#print "$statement \n";

$statement = " rm -f $WORKINGDATAPATH/sub" . $subj[$k] . "/test/data_test0000.nii.gz
$WORKINGDATAPATH/sub" . $subj[$k] . "/test/data_test0031.nii.gz ";
#print "$statement \n";

$statement = " fslmerge -t $WORKINGDATAPATH/sub" . $subj[$k] . "/data_foreddycorrect
$WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0 $WORKINGDATAPATH/sub" . $subj[$k]
. "/test/data_test* ";
#print "$statement \n";

$statement = " eddy_correct $WORKINGDATAPATH/sub" . $subj[$k] . "/data_foreddycorrect
$WORKINGDATAPATH/sub" . $subj[$k] . "/data.nii.gz 0 ";
#print "$statement \n";

################
#### Convert T1 DICOMs, set up T1 directories for analysis
################

$statement = "mkdir $WORKINGDATAPATH/sub" . $subj[$k] . "/t1/ ";
#print "$statement \n";

$statement = " dcm2nii -o $WORKINGDATAPATH/sub" . $subj[$k] . "/t1/ ";
$statement .= " /home/lbradstreet1/robins_dcm/RobinsfMRI/PD*_" . $subj[$k] . "_*/t1*/* ";
#print "$statement \n";

$statement = " mv $WORKINGDATAPATH/sub" . $subj[$k] . "/t1/co*
$WORKINGDATAPATH/sub" . $subj[$k] . "/struct_raw ";
```

```
#print "$statement \n";

$statement = " mv $WORKINGDATAPATH/sub" . $subj[$k] . "/struct_raw.nii.gz
$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/ ";
#print "$statement \n";

$statement = " bet $WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_raw.nii.gz
$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_bet -f .3 -c 83 102 138 -r 68 -m -B";
#print "$statement \n";

$statement = " fast -B -o $WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_fast
$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_bet.nii.gz";
#print "$statement \n";


################
#### Registration between EPI, T1, and MNI152 template
################

$statement = " bet $WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0.nii.gz
$WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0_bet -m -f .35 -g .1 ";
#print "$statement \n";


$statement = " flirt -dof 6 -in $WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0_bet.nii.gz -
ref $WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_fast_restore.nii.gz -omat
$WORKINGDATAPATH/sub" . $subj[$k] . "/dti_6df_2_struct.mat";
#print "$statement \n";


$statement = " flirt -dof 6 -in $WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0_bet.nii.gz -
ref $WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_fast_restore.nii.gz -applyxfm -init
$WORKINGDATAPATH/sub" . $subj[$k] . "/dti_6df_2_struct.mat -out
$WORKINGDATAPATH/sub" . $subj[$k] . "/data_avgb0_6df_2_struct.nii.gz ";
#print "$statement \n";

$statement = " flirt -dof 12 -in $WORKINGDATAPATH/sub" . $subj[$k] .
"/t1/struct_fast_restore.nii.gz -ref $WORKINGDATAPATH/MNI152_T1_1mm_brain.nii.gz -
omat $WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_12df_2_MNI.mat ";
#print "$statement \n";


$statement = " flirt -dof 12 -in $WORKINGDATAPATH/sub" . $subj[$k] .
"/t1/struct_fast_restore.nii.gz -ref $WORKINGDATAPATH/MNI152_T1_1mm_brain.nii.gz -
applyxfm -init $WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_12df_2_MNI.mat -out
$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_12df_2_MNI.nii.gz ";
```

```
#print "$statement \n";

$statement  = " fnirt --in=$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_raw.nii.gz --
ref=$WORKINGDATAPATH/MNI152_T1_1mm.nii.gz --aff=$WORKINGDATAPATH/sub" .
$subj[$k] . "/t1/struct_12df_2_MNI.mat --cout=$WORKINGDATAPATH/sub" . $subj[$k] .
"/t1/struct_warp_2_MNI_warpfield.nii.gz ";
#print "$statement \n";

$statement  = " applywarp --in=$WORKINGDATAPATH/sub" . $subj[$k] .
"/t1/struct_raw.nii.gz --ref=$WORKINGDATAPATH/MNI152_T1_1mm.nii.gz --
warp=$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_warp_2_MNI_warpfield.nii.gz --
out=$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_warp_2_MNI.nii.gz";
#print "$statement \n";

$statement  = " applywarp --in=$WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0_bet.nii.gz -
-ref=$WORKINGDATAPATH/MNI152_T1_1mm_brain.nii.gz --
warp=$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_warp_2_MNI_warpfield.nii.gz --
premat=$WORKINGDATAPATH/sub" . $subj[$k] . "/dti_6df_2_struct.mat --
out=$WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0_warp_2_MNI.nii.gz";
#print "$statement \n";

$statement  = " convert_xfm -omat $WORKINGDATAPATH/sub" . $subj[$k] .
"/struct_6df_2_dti.mat -inverse $WORKINGDATAPATH/sub" . $subj[$k] .
"/dti_6df_2_struct.mat ";
#print "$statement \n";

$statement  = " flirt -dof 6 -in $WORKINGDATAPATH/sub" . $subj[$k] .
"/t1/struct_fast_restore.nii.gz -ref $WORKINGDATAPATH/sub" . $subj[$k] .
"/avgb0_bet.nii.gz -applyxfm -init $WORKINGDATAPATH/sub" . $subj[$k] .
"/struct_6df_2_dti.mat -out $WORKINGDATAPATH/sub" . $subj[$k] .
"/struct_6df_2_avgb0.nii.gz ";
#print "$statement \n";

$statement  = " invwarp -w $WORKINGDATAPATH/sub" . $subj[$k] .
"/t1/struct_warp_2_MNI_warpfield.nii.gz -o $WORKINGDATAPATH/sub" . $subj[$k] .
"/t1/MNI_warp_2_struct_warpfield.nii.gz -r $WORKINGDATAPATH/sub" . $subj[$k] .
"/t1/struct_fast_restore.nii.gz ";
#print "$statement \n";

$statement  = " applywarp --ref=$WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0_bet.nii.gz
--in=$WORKINGDATAPATH/MNI152_T1_1mm_brain.nii.gz --
warp=$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/MNI_warp_2_struct_warpfield.nii.gz --
postmat=$WORKINGDATAPATH/sub" . $subj[$k] . "/struct_6df_2_dti.mat --
out=$WORKINGDATAPATH/sub" . $subj[$k] . "/MNI_warp_2_avgb0.nii.gz";
#print "$statement \n";
```

```
#################
#### Rename old bval and bvec files in each Ss folder
#################

$statement  = " mv $WORKINGDATAPATH/sub" . $subj[$k] . "/bvec
$WORKINGDATAPATH/sub" . $subj[$k] . "/bvec_old ";
#print "$statement \n";

$statement  = " mv $WORKINGDATAPATH/sub" . $subj[$k] . "/bval
$WORKINGDATAPATH/sub" . $subj[$k] . "/bval_old ";
#print "$statement \n";

$statement  = " cp $WORKINGDATAPATH/bvec_new $WORKINGDATAPATH/sub" .
$subj[$k] . "/bvec ";
#print "$statement \n";

$statement  = " cp $WORKINGDATAPATH/bval_new $WORKINGDATAPATH/sub" .
$subj[$k] . "/bval ";
#print "$statement \n";


#################
#### Fitting diffusion tensors
#################

$statement  = " dtifit -k $WORKINGDATAPATH/sub" . $subj[$k] . "/data.nii.gz -o
$WORKINGDATAPATH/sub" . $subj[$k] . "/dti -m $WORKINGDATAPATH/sub" . $subj[$k]
. "/avgb0_bet_mask.nii.gz -r $WORKINGDATAPATH/sub" . $subj[$k] . "/bvec -b
$WORKINGDATAPATH/sub" . $subj[$k] . "/bval ";
#print "$statement \n";


#################
#### Build probability distribution of diffusion at each voxel
#################

$statement  = " mv $WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0_bet_mask.nii.gz
$WORKINGDATAPATH/sub" . $subj[$k] . "/nodif_brain_mask.nii.gz ";
#print "$statement \n";

$statement  = " mv $WORKINGDATAPATH/sub" . $subj[$k] . "/bval
$WORKINGDATAPATH/sub" . $subj[$k] . "/bvals ";
#print "$statement \n";

$statement  = " mv $WORKINGDATAPATH/sub" . $subj[$k] . "/bvec
$WORKINGDATAPATH/sub" . $subj[$k] . "/bvecs ";
```

```perl
#print "$statement \n";

$statement  = " bedpostx $WORKINGDATAPATH/sub" . $subj[$k] . " ";
#print "$statement \n";


################
#### Register template CST ROIs into diffusion space
###############

$statement  = " applywarp --ref=$WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0_bet.nii.gz
--in=$WORKINGDATAPATH/corticospinal_superiorseed_R.nii.gz --
warp=$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/MNI_warp_2_struct_warpfield.nii.gz --
postmat=$WORKINGDATAPATH/sub" . $subj[$k] . "/struct_6df_2_dti.mat --interp=nn --
out=$WORKINGDATAPATH/sub" . $subj[$k] .
"/corticospinal_superiorseed_R_warp_2_avgb0.nii.gz";
#print "$statement \n";

$statement  = " fslmaths $WORKINGDATAPATH/sub" . $subj[$k] .
"/corticospinal_superiorseed_R_warp_2_avgb0.nii.gz -bin $WORKINGDATAPATH/sub" .
$subj[$k] . "/corticospinal_superiorseed_R_warp_2_avgb0.nii.gz";
#print "$statement \n";

$statement  = " applywarp --ref=$WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0_bet.nii.gz
--in=$WORKINGDATAPATH/corticospinal_superiorseed_L.nii.gz --
warp=$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/MNI_warp_2_struct_warpfield.nii.gz --
postmat=$WORKINGDATAPATH/sub" . $subj[$k] . "/struct_6df_2_dti.mat --interp=nn --
out=$WORKINGDATAPATH/sub" . $subj[$k] .
"/corticospinal_superiorseed_L_warp_2_avgb0.nii.gz";
#print "$statement \n";

$statement  = " fslmaths $WORKINGDATAPATH/sub" . $subj[$k] .
"/corticospinal_superiorseed_L_warp_2_avgb0.nii.gz -bin $WORKINGDATAPATH/sub" .
$subj[$k] . "/corticospinal_superiorseed_L_warp_2_avgb0.nii.gz";
#print "$statement \n";

$statement  = " applywarp --ref=$WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0_bet.nii.gz
--in=$WORKINGDATAPATH/corticospinal_inferiorseed_R.nii.gz --
warp=$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/MNI_warp_2_struct_warpfield.nii.gz --
postmat=$WORKINGDATAPATH/sub" . $subj[$k] . "/struct_6df_2_dti.mat --interp=nn --
out=$WORKINGDATAPATH/sub" . $subj[$k] .
"/corticospinal_inferiorseed_R_warp_2_avgb0.nii.gz";
#print "$statement \n";

$statement  = " fslmaths $WORKINGDATAPATH/sub" . $subj[$k] .
"/corticospinal_inferiorseed_R_warp_2_avgb0.nii.gz -bin $WORKINGDATAPATH/sub" .
$subj[$k] . "/corticospinal_inferiorseed_R_warp_2_avgb0.nii.gz";
```

```
#print "$statement \n";

$statement  = " applywarp --ref=$WORKINGDATAPATH/sub" . $subj[$k] . "/avgb0_bet.nii.gz
--in=$WORKINGDATAPATH/corticospinal_inferiorseed_L.nii.gz --
warp=$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/MNI_warp_2_struct_warpfield.nii.gz --
postmat=$WORKINGDATAPATH/sub" . $subj[$k] . "/struct_6df_2_dti.mat --interp=nn --
out=$WORKINGDATAPATH/sub" . $subj[$k] .
"/corticospinal_inferiorseed_L_warp_2_avgb0.nii.gz";
#print "$statement \n";

$statement  = " fslmaths $WORKINGDATAPATH/sub" . $subj[$k] .
"/corticospinal_inferiorseed_L_warp_2_avgb0.nii.gz -bin $WORKINGDATAPATH/sub" .
$subj[$k] . "/corticospinal_inferiorseed_L_warp_2_avgb0.nii.gz";
#print "$statement \n";

#################
#### Rename CST files to include file extension .txt.
#################

$statement  = " mv $WORKINGDATAPATH/sub" . $subj[$k] . "/corticospinal_seed_R
$WORKINGDATAPATH/sub" . $subj[$k] . "/corticospinal_seed_R.txt ";
#print "$statement \n";

$statement  = " mv $WORKINGDATAPATH/sub" . $subj[$k] . "/corticospinal_seed_L
$WORKINGDATAPATH/sub" . $subj[$k] . "/corticospinal_seed_L.txt ";
#print "$statement \n";

#################
#### Probabilistic tractography for corticospinal tract
#################

$statement  = " probtrackx --network --mode=seedmask -s $WORKINGDATAPATH/sub" .
$subj[$k] . ".bedpostX/merged ";
$statement .= " -m $WORKINGDATAPATH/sub" . $subj[$k] . "/nodif_brain_mask.nii.gz ";
$statement .= " -x $WORKINGDATAPATH/sub" . $subj[$k] .
"/corticospinal_inferiorseed_R_warp_2_avgb0.nii.gz" ;
$statement .= " --waypoints=$WORKINGDATAPATH/sub" . $subj[$k] .
"/corticospinal_superiorseed_R_warp_2_avgb0.nii.gz";
$statement .= " -l -c 0.2 -S 2000 --steplength=0.5 -P 5000 --fibthresh=0.1 --randfib=0 ";  ####
Will run first with 5 samples to test, then 5000
$statement .= " --forcedir --opd ";
$statement .= " --dir=$WORKINGDATAPATH/sub" . $subj[$k] .
".bedpostX/corticospinal_tractography_R/";
print "$statement \n";
```

```
$statement  = " probtrackx --network --mode=seedmask -s $WORKINGDATAPATH/sub" .
$subj[$k] . ".bedpostX/merged ";
$statement .= " -m $WORKINGDATAPATH/sub" . $subj[$k] . "/nodif_brain_mask.nii.gz ";
$statement .= " -x $WORKINGDATAPATH/sub" . $subj[$k] .
"/corticospinal_inferiorseed_L_warp_2_avgb0.nii.gz" ;
$statement .= " --waypoints=$WORKINGDATAPATH/sub" . $subj[$k] .
"/corticospinal_superiorseed_L_warp_2_avgb0.nii.gz";
$statement .= " -l -c 0.2 -S 2000 --steplength=0.5 -P 5000 --fibthresh=0.1 --randfib=0 ";  ####
Will run first with 5 samples to test, then 5000
$statement .= " --forcedir --opd ";
$statement .= " --dir=$WORKINGDATAPATH/sub" . $subj[$k] .
".bedpostX/corticospinal_tractography_L/";
print "$statement \n";



################
####  Tractography for significant blob in tbss12 tstat10
################


#### Will run first with 5 samples to test, then 5000##


$statement  = " probtrackx --network --mode=seedmask -s $WORKINGDATAPATH/sub" .
$subj[$k] . ".bedpostX/merged ";
$statement .= " -m $WORKINGDATAPATH/sub" . $subj[$k] . "/nodif_brain_mask.nii.gz ";
$statement .= " -x $WORKINGDATAPATH/tbss/stats/" . $subj[$k] .
"_dti_FA_FA_tbss12_tfce_corrp_tstat10_thr95.nii.gz" ;
$statement .= " -l -c 0.2 -S 2000 --steplength=0.5 -P 5000 --fibthresh=0.1 --randfib=0 ";
$statement .= " --forcedir --opd ";
$statement .= " --dir=$WORKINGDATAPATH/sub" . $subj[$k] .
".bedpostX/tbss12_tstat10_significantblob/";
#print "$statement \n";



################
####  Registration: Native space to MNI space for Tractography for significant blob in tbss12
tstat10
################


$statement  = " applywarp --in=$WORKINGDATAPATH/sub" . $subj[$k] .
".bedpostX/tbss12_tstat10_significantblob/fdt_paths_thr01.nii.gz --
ref=$WORKINGDATAPATH/MNI152_T1_1mm_brain.nii.gz --
warp=$WORKINGDATAPATH/sub" . $subj[$k] . "/t1/struct_warp_2_MNI_warpfield.nii.gz --
premat=$WORKINGDATAPATH/sub" . $subj[$k] . "/dti_6df_2_struct.mat --
```

out=$WORKINGDATAPATH/sub" . $subj[$k] .
".bedpostX/tbss12_tstat10_significantblob/fdt_paths_thr01_dti_2_MNI.nii.gz";
#print "$statement \n";

################
Set up directory for creating composite image of tractography for significant blob in tbss12
tstat10
################

$statement = " mkdir $WORKINGDATAPATH/tractographytbss12tstat10 ";
#print "$statement \n";

$statement = " cp $WORKINGDATAPATH/sub" . $subj[$k] .
".bedpostX/tbss12_tstat10_significantblob/fdt_paths_thr01_dti_2_MNI_bin.nii.gz
$WORKINGDATAPATH/tractographytbss12tstat10/sub" . $subj[$k] .
"_fdt_paths_thr01_dti_2_MNI_bin.nii.gz ";
#print "$statement \n";

################
Copy significant cluster from tbss12 tstat10 in each participant's DTI space to FAvalues
folder
################

$statement = " cp $WORKINGDATAPATH/tbss/stats/" . $subj[$k] .
"_dti_FA_FA_tbss12_tfce_corrp_tstat10_thr95.nii.gz $WORKINGDATAPATH/FAvalues ";
#print "$statement \n";

################
Binarize significant cluster mask from tbss12 tstat10 for each participant in FAvalues
folder
################

$statement = " fslmaths $WORKINGDATAPATH/FAvalues/" . $subj[$k] .
"_dti_FA_FA_tbss12_tfce_corrp_tstat10_thr95.nii.gz -bin
$WORKINGDATAPATH/FAvalues/" . $subj[$k] .
"_dti_FA_FA_tbss12_tfce_corrp_tstat10_thr95_bin.nii.gz ";
#print "$statement \n";

################
Multiply binarized significant cluster mask from tbss12 tstat10 for each participant by each
participants FA value image in FAvalues folder
################

$statement = " fslmaths $WORKINGDATAPATH/FAvalues/" . $subj[$k] .
"_dti_FA_FA_tbss12_tfce_corrp_tstat10_thr95_bin.nii.gz -mul

```
$WORKINGDATAPATH/FAvalues/" . $subj[$k] . "_dti_FA.nii.gz
$WORKINGDATAPATH/FAvalues/" . $subj[$k] . "_tbss12cluster_FA.nii.gz ";
#print "$statement \n";



                }
```