ABSTRACT

Title of dissertation: WHITE MATTER CONNECTIVITY AND SOCIAL COGNITIVE IMPAIRMENT IN A TRANSDIAGNOSTIC SAMPLE

Kristen Dwyer, Doctor of Philosophy, 2018

Dissertation directed by: Professor Jack Blanchard, Ph.D.

Department of Psychology

Social cognitive deficits are impaired mental operations underlying social interactions and are present across psychotic disorders, including schizophrenia spectrum, bipolar, and depressive disorders. It is unclear what neurobiological factors underlie social cognitive impairment, though one possibility is that impaired white matter connections within social cognitive cerebral networks may give rise to social cognitive impairment in psychosis. This study extended current diffusion tensor imaging (DTI) research to a transdiagnostic sample of individuals with psychotic disorders and controls and employed a Research Domain Criteria (RDoC) multiple units of analysis approach. The current study aimed to (1) assess the relation between social cognition (theory of mind and emotion processing), social functioning, negative symptoms, and general cognitive ability, and (2) examine white matter integrity within the uncinate fasciculus

(UF) and inferior longitudinal fasciculus (ILF) through fractional anisotropy (FA) values, and to investigate their relation to social cognition and social functioning.

Thirty-three participants, 25 with a history of clinically significant psychotic symptoms and 8 controls, completed the research project. Results indicated that social cognition was positively related to general cognitive ability, but not social functioning. However, better theory of mind was related to improved community functioning. Negative symptoms were differentially related to social cognition as there was only a negative association between theory of mind and expressive negative symptoms. More severe negative symptoms were associated with poorer social functioning and cognitive ability. White matter integrity within either identified tract did not contribute to social cognitive ability. Although FA within the left ILF was related to overall functioning and social functioning and FA within the left UF was related to community functioning, these relationships were in the opposite direction as originally predicted with better functioning contributing to lower FA.

This is the first study to investigate white matter microstructure in a transdiagnostic sample using an RDoC approach. Our results indicate that there may be unique challenges involved in implementing RDoC. We encourage future researchers to recruit larger sample sizes, administer several behavioral measures of interest to create latent variables, and consider novel imaging methods to better address the difficulties associated with crossing fiber tracts.

WHITE MATTER CONNECTIVITY AND SOCIAL COGNITIVE IMPAIRMENT IN A TRANSDIAGNOSTIC SAMPLE

By

Kristen Renee Dwyer

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, College Park in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2018

Advisory Committee:
Professor Jack Blanchard, Chair
Associate Professor Andres De Los Reyes
Professor Ellen Fabian (Dean's Representative)
Associate Professor Tracy Riggins
Assistant Professor Alexander Shackman

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

Chapter 1: Introduction

Social impairment in psychosis-related disorders, such as schizophrenia, contributes to functional impairment, including decreased rates of employment, lower academic achievement, fewer and lower quality relationships, and less independent living (Allen, Frantom, Strauss, & van Krammen, 2005; Harvey et al., 2012; Kirkpatrick, Fenton, Carpenter, & Marder, 2006; Marwaha & Johnson, 2004). Despite effective treatments for psychotic symptoms, functional and social impairments treatment needs are unmet. In schizophrenia, less than 20% of patients achieve functional recovery, only 10 to 20% are employed, and 50% receive disability compensation within 6 months of receiving a diagnosis (Harvey et al., 2012; Marwaha & Johnson, 2004). In addition to functional difficulties, reduced social support impacts physical health wherein perceived loneliness and social isolation lead to a 26% and 29% increased likelihood of mortality, respectively (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015). Symptoms, such as social anhedonia and asociality, not only impact the individual, but also family members as these symptoms contribute to increased family discord and conflict (e.g., high expressed emotion; Butzlaff & Hooley, 1998) and are a source of caregiver burden (Dyck, Short, & Vitaliano, 1999).

Social impairment is often evident prior to the full onset of a psychotic disorder. Research shows that individuals at clinical high risk for developing a psychotic disorder often exhibit social and role functioning deficits, including social withdrawal, poor social skills, and a decline in academic performance (Bellack, Morrison, Wixted, & Mueser, 1990; Rosenheck, et al., 2006). Moreover, longitudinal studies have demonstrated that social isolation and withdrawal are the most common symptoms seen in individuals at risk for developing a psychotic disorder (Lencz, Smith, Auther, Correll, & Cornblatt, 2004), that these social impairments manifest roughly two to four years prior to the first psychiatric hospitalization (Häfner, Nowotny, Löffler, an der Heiden, & Maurer, 1995), and that poor social functioning in clinical high risk individuals predicts conversion to psychosis (Cannon et al., 2008). Additionally, research with nonclinical samples indicates that impaired social skills and social withdrawal are also predictive of the development of depression (Katz, Conway, Hammen, Brennan, & Najman, 2011). Given that the onset of psychosis-related disorders typically occurs during late adolescence, a critical period of social skill development with people outside of the home, the disruption of skills acquisition and relationship formation can have long-lasting effects. Therefore, understanding the mechanisms underlying social dysfunction is imperative in addressing the public and personal health costs in psychotic disorders.

One factor which may contribute to social deficits is cognitive impairment. Longitudinal studies of individuals at clinical high risk for psychosis have shown widespread cognitive impairments when compared to matched controls (Fusar-Poli et al., 2012; Giuliano et al., 2012), which is evidenced as early as age eight (Roalf et al., 2014). Additionally, more severe cognitive deficits are seen in individuals who transition to a psychotic disorder than those who do not (Giuliano et al., 2012). After transition, these cognitive impairments remain stable throughout the course of illness, even in cases in which an individual experiences a remission of psychotic symptoms (Harvey, Docherty, Serper, & Rasmussen, 1990). Cognitive impairment has been shown to predict functional decline (Velligan et al., 1997), including impaired social skills, and is consistently related cross-sectionally to negative symptoms (Harvey, Koren, Reichenberg, & Bowie, 2006), which at their core, are symptoms of social dysfunction. However, cognitive ability only accounts for approximately 9% of the variance in negative symptoms, and researchers have concluded that cognition and social impairment are separable clinical features of schizophrenia spectrum disorders (Harvey et al., 2006).

Beyond general cognitive ability, a more proximal contributor to social impairment within psychotic disorders may be social cognition. Social cognition is defined as specific neurocognitive processes involving the perception, interpretation, and processing of social information (Green et al., 2008). Specific skill sets that social cognition encompasses typically include emotion processing, social perception, theory of mind, and attributional style (Couture, Penn, & Roberts, 2006). Emotion processing involves the ability to recognize others' emotions, facial expressions, and vocal prosody, as well as manage one's own emotions (Couture et al., 2006; Edwards, Pattison, Jackson, & Wales, 2001; Pinkham et al., 2014). Social perception refers to the ability to interpret social cues, and is closely linked to social knowledge, which involves understanding social rules, goals, and conventions (Couture et al., 2006; Pinkham et al., 2014). Theory of mind involves the ability to represent others' mental states and make correct inferences about others' mental states, intentions, and beliefs (Couture et al., 2006; Pinkham et al., 2014). Attributional style describes how individuals assign causality to social interactions (Pinkham et al., 2014).

Although social cognition is often significantly correlated with general cognitive ability, researchers agree that it is a distinct construct (Sergi et al., 2007). A recent systematic review of factor analytic studies demonstrated that six of nine studies found social cognition and general cognitive ability to be distinct factors (Mehta et al., 2013). Two studies found cross-loadings between the two constructs and one study suggested that social cognition and general cognitive ability are best explained by a unitary cognitive deficit factor. However, these three studies were criticized for reporting a single cognitive factor or using only one social cognitive assessment. Additionally, studies using correlational and structural equation modeling analyses have found that social cognition mediates the relation between cognitive ability and community functioning in schizophrenia, indicating that social cognition may be more closely related to functioning than cognition (Brekke, Kay, Lee, & Green, 2005; Sergi, Rassovsky, Nuechterlein, & Green, 2006).

Social cognition deficits are a transdiagnostic feature as research has revealed that individuals with schizophrenia (Edwards et al., 2001), depressive (Weightman, Air, & Baune, 2014), and bipolar (Samame, Martino, & Strejilevich, 2012) disorders evidence impairments in social cognitive ability. Although most heavily studied in schizophrenia samples wherein individuals typically exhibit impairment across all social cognition domains, recent research indicates that deficits in theory of mind and emotion processing are present both in individuals with depressive and bipolar disorders (Samame et al., 2012; Weightman et al., 2014). There is evidence of a continuum of emotion processing abilities across diagnoses as findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes study indicate that there are progressively increased emotion identification deficits compared to controls from bipolar disorder to schizoaffective disorder to schizophrenia (Ruocco et al., 20014). Importantly, social cognitive difficulties can precede disorder onset (Chung, Kang, Shin, Yoo, & Kwon, 2008), are present early on in illness (Bertrand, Sutton, Achin, Malia, & Legpage, 2007), are relatively stable (Green & Horan, 2010), and are evident during periods of symptomatic remission (Samame et al., 2012; Weightman et al., 2014).

Given that adequate social cognition is required to rapidly and correctly process social stimuli, it is not surprising that deficits in social cognitive ability have been associated with decreased community functioning, impaired social skill, and higher levels of negative symptoms (Browne et al., 2016; Couture, Granholm, & Fish, 2011; Couture et al., 2006; Horan et al., 2011; Pinkham, Penn, Green, & Harvey, 2016). A review of the relation between functional outcome and social cognition impairments within individuals with schizophrenia suggests that functional outcomes are consistently and modestly related to social perception and emotion perception (Couture et al., 2006). Although less frequently studied, the review also notes that theory of mind is associated with social skill ability. More recent work has suggested that social cognitive bias, defined as specific patterns in open-ended interpretations of social situations, contributes to poorer social functioning as well as greater levels of psychiatric symptoms known to impact functioning, such as positive symptoms (e.g., paranoia and suspiciousness) and negative symptoms (e.g., social disengagement) (Buck et al., 2016). Additionally, there is evidence of a link between social cognition (theory of mind) and poor functional outcomes in individuals with mood disorders (Inoue, Yamada, & Kanba, 2006).

Pharmacological trials and intervention research have established that antipsychotic medications do not improve social cognition (Gray & Roth, 2007; Penn et al., 2009) and that psychosocial interventions are only minimally effective at ameliorating deficits in affect recognition and theory of mind (Fiszdon & Reddy, 2012). Moving forward, it will be critical to examine mechanisms that contribute to these deficits. One possible avenue is to examine neural mechanisms to more closely target the therapeutic needs of individuals experiencing social dysfunction (Devries, Glasper, & Detillion, 2003; House, Landis, & Umberson 1988).

Psychotic disorders, such as schizophrenia, are considered to be neurodevelopmental disorders (Lewis & Levitt, 2002; Murray, O'Callaghan, Castle, & Lewis, 1992; Rapoport & Gogtay, 2011); therefore, a close examination of the neural mechanisms of social cognitive and functioning impairments is recommended. Neurodevelopmental models suggest that genetic and environmental factors exert an influence during prenatal, perinatal, and early adolescent periods, which lead to disorder onset in late adolescence and young adulthood. Examples of environmental factors that may influence disorder onset include maternal diabetes, low birth weight, older paternal age, winter birth, maternal stress, growing up in an urban environment, traumatic events early in life, and regular cannabis use (King, St-Hilaire, & Heidkamp, 2010; van Os, Kenis, & Rutten, 2010). Neural abnormalities seen among individuals with schizophrenia spectrum disorders include enlarged ventricles (Rapoport et al., 1997; Weinberger & Wyatt, 1983), reduced grey matter volume (Fornito, Yucel, Patti, Wood, & Pantelis, 2009), and disorganization of hippocampal neurons (Conrad, Abebe, Austin, Forsythe, & Scheibel, 1991). Furthermore, during adolescence, individuals with schizophrenia evidence increased rates of pruning across grey matter in comparison to non-clinical adolescents (Feinberg, 1982). More recently, white matter abnormalities have also been found in schizophrenia samples. Postmortem studies have shown reduced cellular density and integrity of oligodendrocytes, particularly in white matter tracts connecting with the prefrontal cortices (Uranova, Vostrikov, Orlovskaya, & Rachmanova, 2004). Structural neuroimaging studies suggest that reduced white matter integrity precedes disorder onset (Karlsgodt, Niendam, Bearden, & Cannon, 2009) and that individuals with childhood-onset schizophrenia evidence 2% slower white matter growth per year in comparison to healthy controls (Gogtay et al., 2008). Social cognitive and functioning abilities rely upon intact connections between the prefrontal cortices and limbic system structures, so adequate integrity of these white matter tracts is imperative for behavioral success.

Neuroimaging and lesion studies have localized cerebral regions involved in social cognitive processes, specifically, theory of mind and emotion processing. These include the medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC), temporo-parietal junction (TPJ), posterior superior temporal sulcus (pSTS), and temporal poles for theory of mind (Amodio & Frith, 2006; Bahnemann, Dziobek, Prehn, Wolf, & Heekeren, 2010; Mar, 2011). Emotion processing is dependent on functional integrity of the amygdala, hippocampus, thalamus, fusiform gyrus, OFC, STS, and temporal poles (Adolphs, Tranel, Damasio, & Damasio, 1994; Brunet-Gouet & Decety, 2006; Carter et al., 2009; Hornak, Rolls, & Wade, 1996). The amygdala, in particular, is critical in distinguishing different facial emotions (Morris et al., 1998). These regions form the social brain networks, which rely on white matter to interconnect them (Carrington & Bailey, 2009; Van Overwalle, 2009). Research in schizophrenia shows that the MPFC and TPJ show significantly less activity in comparison to healthy controls during fMRI tasks assessing theory of mind (Das, Lagopoulos, Coulston, Henderson, & Malhi, 2012; Walter et al., 2009). Additionally, when engaging in emotion processing tasks, individuals with schizophrenia typically show decreased activation in the amygdala, OFC, and STS (Gur et al., 2002; Habel et al., 2004; Vuilleumier & Pourtois, 2007). However, neuroimaging findings have not been consistent. Some researchers have found increased activation within the MPFC during theory of mind tasks (Brune et al., 2008) and increased activation within the amygdala during emotion processing tasks (Pankow et al., 2013).

We hypothesize that reduced integrity of white matter connections in brain regions implicated in social cognitive tasks may underlie the abnormal fMRI findings in schizophrenia. Specifically, we suggest that disrupted connectivity may reduce the functional integrity of the widely distributed networks involved in social cognition. Lesion studies show interruption of structural connections between the amygdala and prefrontal and temporal regions leads to deficits in the social, emotional, cognitive, and perceptual processing similar to that observed in schizophrenia. Specifically, the interruption of the uncinate fasciculus (UF), a white matter tract that intersects the OFC and the anterior and medial temporal lobes, including the amygdala (Ghashghaei & Barbas, 2002; Ghashghaei, Hilgetag, & Barbas, 2007; Von Der Heide, Skipper, Klobusicky, & Olson, 2013), has been implicated in the development of deficits in social cognition (Jalbrzikowski et al., 2014). The inferior longitudinal fasciculus (ILF) may play a more specific role in social tasks requiring emotion recognition and is a tract that connects the occipital lobe and posterior lingual and fusiform cortices to the lateral and medial temporal cortex near the amygdala and parahippocampal gyrus (Amaral & Price, 1984; Catani, Jones, & Donato, 2003; Iwai & Yukie, 1987; Latini, 2015). Recent work investigating white matter integrity among these tracts has found that reductions in fractional anisotropy (FA; a measure of the directionality and density of fiber tracts in a voxel that is higher along well-defined tracts and sensitive to white matter microstructural changes) of the ILF is associated with impairment in facial emotion recognition in a schizophrenia sample (Miyata et al., 2010) as well as never medicated patients with first-episode psychosis (Zhao et al., 2017), and that decreased axial diffusion (a measure of diffusivity along the principal axis) in the left UF is related to impaired performance on theory of mind and emotion perception tasks in individuals at genetic risk for developing psychosis (Jalbrzikowski et al., 2014). Furthermore, lower FA in the ILF has been shown to be predictive of both social and role functioning deterioration in individuals at ultra-high risk for developing psychosis (Karlsgodt, Niendam, Bearden, & Cannon, 2009). Complementing this study, Krakauer and colleagues (2017) found that social and occupational functioning was positively correlated with FA in the left ILF among ultra-high risk individuals. Although a meta-analytic study of white matter integrity in individuals with bipolar disorder and schizophrenia demonstrated no significant FA differences between the two disorders (Dong et al., 2017), to date, there has been no examination of the relation between white matter connectivity, social cognition, and social functioning among individuals with depressive or bipolar disorders. Therefore, we aim to extend current work through an examination of white matter integrity and social functioning correlates of these tracts in a transdiagnostic sample.

The Current Study

We addressed an important gap in the literature by studying the anatomical connectivity among social cognitive cerebral networks across clinical outpatients using diffusion tensor imaging (DTI). Consistent with the Research Domain Criteria (RDoC;

Insel et al., 2010) multiple-levels of analysis approach, the current study examined social cognition and social functioning transdiagnostically across three RDoC units of analysis, including circuits (DTI), paradigms (behavioral theory of mind and emotion processing tasks), and self-report (community functioning). This study examined whether disrupted white matter connections predict deficits in theory of mind, emotion processing, and real world functioning in a diverse clinical sample. Specifically, the following preliminary aim, three primary aims, and two exploratory aims were examined:

Preliminary Aim: Examine the relation between social cognition (theory of mind and emotion processing), social functioning, negative symptoms, and general cognitive ability.

Hypothesis: We hypothesized that social cognitive ability would be negatively related to negative symptoms and positively related to social functioning and general cognitive ability. Further, it was expected that negative symptoms would be negatively associated with social functioning and general cognitive ability. Lastly, we predicted that more severe cognitive impairment would be related to poorer social functioning.

Aim 1: Examine the relation between social cognition (theory of mind and emotion processing) and white matter microstructure (FA in the uncinate fasciculus and inferior longitudinal fasciculus).

Hypothesis: It was hypothesized that white matter integrity, as reflected by FA in the uncinate fasciculus, would be positively associated with theory of mind performance, and that FA in the inferior longitudinal fasciculus and uncinate fasciculus would be positively associated with emotion processing performance.

Aim 2: Examine the association between white matter microstructure and clinical assessments of social functioning in the community.

Hypothesis: We hypothesized that FA in the uncinate fasciculus and inferior longitudinal fasciculus would be positively associated with social functioning in the community.

Exploratory Aim 1: Examine the contribution of white matter microstructure within the uncinate fasciculus and inferior longitudinal fasciculus to general cognitive ability.

Hypothesis: It was hypothesized that, in comparison to social cognition, general cognitive ability would not account for a significant amount of variance within FA in the uncinate fasciculus and inferior longitudinal fasciculus.

Exploratory Aim 2: To address other possible cerebral white matter networks involved in social cognition, we will employ a whole brain analysis approach. Exploratory analyses were conducted to evaluate alternative cerebral white matter tracts.

Chapter 2: Methods

Participants

Participants (N=39: 30 with a history of clinically significant psychotic symptoms and 9 demographically-matched control participants) for this study were recruited from clinics affiliated with the University of Maryland School of Medicine that typically have a range of psychosis-related disorders present including schizophrenia, schizoaffective disorder, other psychotic disorders, bipolar disorder, major depression, and past substance use disorders. Of note, one control and five clinical participants were excluded from the neuroimaging analyses (final N=33) due to the following reasons: three did not pass safety screening, two exited the scanner prematurely, and one had a neurologic anomaly. Building on the conceptual framework of RDoC, recruitment was not restricted to any specific DSM-5 diagnostic category. Rather, we recruited clinical participants broadly but limited recruitment to those with a history of clinically significant primary psychotic symptoms (i.e., a history of psychotic symptoms that are not secondary to substances or a medical condition).

For study inclusion, participants were 1) between the ages of 18-60, 2) referred from outpatient clinician 3) literate and fluent in English, 4) had normal or corrected-to normal vision with contact lenses, 5) no history of serious head injury, 6) no evidence of IQ < 70 (based on WTAR) 7) willing to have assessments videotaped, and 8) if on medications, had a stable regimen for at least 4 weeks. Potential participants were excluded if they 1) had magnetic resonance imaging contraindications (e.g., MR unsafe metal in the body), 2) claustrophobia, 3) history of neurological conditions, 4) exceeded the weight limitations of the scanner, 5) back problems that would prevent the participant from lying on their back for up to 1 hour, and 6) history of substance abuse or dependence within the past 6 months. Additional exclusion criteria for controls included 1) having a known psychological condition, including depression, PTSD, clinical anxiety, and ADHD, 2) family history of psychosis in a first- or second-degree relative, and 3) taking psychoactive drugs, including Zoloft, Ritalin, etc. Recruitment followed and extended upon strategies that have been used in prior studies of conducted at the University of Maryland School of Medicine, which have been effective in recruiting both clinical and non-clinical participants from the medical center and the community. Recruitment methods included both medical record review and referrals from hospital and community clinicians.

Measures

Trained graduate students or master's level research assistants administered measures to establish diagnostic criteria and characterize the sample in terms of symptoms, cognition, and functioning.

<u>*Clinical Interview Measures*</u>

Structured Clinical Interview for DSM-5 (SCID-5). The SCID-5 (First, Williams, Karg, & Spitzer, 2015) is a semi-structured interview that will be used to confirm clinically significant psychotic symptoms. Various sources of information were used to confirm diagnoses (e.g., patient record, medical records, and treatment providers). The SCID-5 was developed for use in research by trained clinicians and includes obligatory questions, operational criteria from the DSM-5, a categorical system for rating symptoms, and an algorithm for arriving at a final diagnosis. If a participant had received a SCID in the past five years, he/she did not need to complete another one. However, if the participant had not received a SCID in the past five years, this measure was included in the assessment battery.

Clinical Assessment Interview for Negative Symptoms (CAINS). The CAINS (Kring, Gur, Blanchard, Horan, & Reise, 2013) is a 13-item semi-structured interview that evaluates negative symptoms in schizophrenia (see Appendix A). Items are rated on a 5-point Likert scale, ranging from 0 (*no impairment*) to 4 (*severe deficit*). The assessment consists of two factors: Expression (EXP; 4 items) and Motivation and Pleasure (MAP; 9 items). The scales have demonstrated good internal consistency (α = .88 for EXP, .74 for MAP), test-retest reliability (r = .69 for both scales), and inter-rater reliability (average ICC = .77 for EXP, .93 for MAP; Kring et al., 2013). The CAINS also demonstrates good convergent and discriminant validity (Kring et al., 2013). All study interviewers were trained and supervised by one of the developers of the CAINS (JJB).

Brief Psychiatric Rating Scale (BPRS). The BPRS (Overall & Gorham, 1962; Ventura et al., 1993) is a 24-item clinician-rated measure that assesses clinical psychiatric symptoms (e.g., somatic concern, suicidality, unusual thought content, suspiciousness) experienced over the previous week (see Appendix B). Items are rated on a 7-point Likert scale, ranging from 1 (*not present*) to 7 (*extremely severe*). Following the factor structure supported by Kopelowicz and colleagues (2008), four subscale scores (Positive Symptoms, Agitation/Mania, Negative Symptoms, Depression/Anxiety) were utilized to assess current level of psychopathology and psychotic symptoms. The BPRS is used extensively in psychiatric research and has well-established psychometric properties

(Anderson, et al., 1989; Morlan & Tan, 1998; Overall & Gorham, 1962).

<u>Assessment of Functioning</u>

Specific Level of Functioning Scale (SLOF). The SLOF (Schneider & Struening, 1983) assesses community functioning (including subscales tapping interpersonal relationships, community living skills, and work skills; see Appendix C). The SLOF is a 30-item semi-structured interview, and items are rated on a 5-point Likert scale, ranging from 1 (*highly untypical*) to 5 (*highly typical*). The 30 SLOF items can be summed for measure of general psychosocial functioning. Additionally, interpersonal relationships and social acceptability items can be summed for a measure of social functioning (SLOF Social) and the activities and work skills item can be summed for a measure of community functioning (SLOF Community). The SLOF performed well in the NIMH grant "*Validation of Measures of Real-World Outcome*" and has been judged to be the best available measure of real-world functioning (Harvey et al., 2011).

<u>Cognitive Assessments</u>

Wechsler Test of Adult Reading (WTAR). The WTAR (Wechsler, 2001) allows you to measure levels of intellectual functioning for individuals ages 16 to 89 years (see Appendix D). For this task, participants are asked to read 50 words aloud, one at a time. The total score is the number of words read correctly. Overall intelligence is estimated using the Full Scale Intelligence Quotient (FSIQ) from the WTAR. WTAR scores were shown to correlate highly with measures of verbal IQ (r = .75), verbal comprehension (r = .74), and full scale IQ (r = .73; Spreen & Strauss, 2006). This assessment was used for inclusion/exclusion criteria as participants were excluded if their estimated FSIQ was below 70.

The Brief Cognitive Assessment Tool for Schizophrenia (B-CATS). The B-CATS (Hurford, Marder, Keefe, Reise, & Bilder, 2011) includes 3 tests to assess cognitive functioning: (1) trails making test B, (2) category fluency, and (3) digit symbol test, and reflects overall cognitive functioning. Administration of the B-CATS requires approximately 10-11 minutes and was selected as an alternative to a comprehensive cognitive battery that are often greater than 90 minutes in duration in order to reduce participant burden. The results of the three tests are combined to form a total score of general cognitive ability. The B-CATS has good convergent validity in that it correlates .86 with more comprehensive cognitive batteries that have been used in schizophrenia samples; correlations between the B-CATS and the comprehensive batteries without the B-CATS tests range from .73 to .82 (Hurford et al., 2011).

Behavioral Assessments of Social Cognition

The Hinting Task. The Hinting Task (Corcoran, Mercer, & Frith, 1995) examines the ability of individuals to infer the true intent of indirect speech and is a measure of theory of mind (see appendix E). Ten short passages present an interaction between 2 characters, and each passage ends with one of the characters dropping a hint. Passages are read aloud by the experimenter, and participants are asked what the character truly meant. If the first response provided is inaccurate, a second hint is delivered, allowing participants to earn partial credit for that passage. Total scores ranged from 0 to 20. The Social Cognition Psychometric Evaluation (SCOPE; Pinkham, Penn, Green, & Harvey, 2016) found that the Hinting Task shows strong psychometric properties, including associations with social and functional outcomes. The Hinting Task was deemed the most psychometrically sound measure of theory of mind and is recommended for use in clinical trials by the SCOPE research team.

Bell Lysaker Emotion Recognition Task (BLERT). The BLERT (Bryson, Bell, & Lysaker, 1997) measures the ability to correctly identify 7 emotional states: happiness, sadness, fear, disgust, surprise, anger, or no emotion (see Appendix F). Participants view 21 10-second video clips of a male actor, providing dynamic facial, vocal-tonal, and upper-body movement cues. After viewing each video, participants identify the expressed emotion. Performance is indexed as the total number of correctly identified emotions (ranging from 0 to 21). SCOPE (Pinkham, Penn, Green, & Harvey, 2016) also concluded that the BLERT shows strong psychometric properties, including modest correlations with social and functional outcomes. The BLERT was deemed the most psychometrically sound measure of emotion processing and is recommended for use in clinical trials by the SCOPE research team.

Procedure

The study was conducted at the University of Maryland School of Medicine (Baltimore) and the Maryland Neuroimaging Center (MNC) over the course of two visits. Prior to study visits, participants were screened for exclusion criteria by chart review, referring clinician, and/or phone. The first visit involved completing the informed consent process, interviews and questionnaires to assess demographic information, diagnosis, symptom severity, social cognition, social and community functioning, and cognitive ability. We used existing protocols to establish competency to provide informed consent in all screened participants. The second visit at the MNC occurred approximately

1 week after the first visit, or sooner, and it involved an MRI safety evaluation and the brain-imaging paradigm. Participants were provided with transportation to the MNC or reimbursement for gas mileage if they chose to drive themselves to the second visit. After participants completed the MNC MRI Safety Screening Questionnaire, they were made familiar with a mock MRI scanner to expose participants to the scanning environment and provide a chance for participants to decide whether they would feel comfortable completing a real scan. Then, a respiration belt was attached around the chest and a heart rate pulse oximeter was attached to the index finger of the non-dominant hand. Finally, participants completed the DTI scanning protocol. The first visit lasted approximately three hours and the second visit lasted approximately one and a half hours. At the end of the study, participants received $75.00 for their study compensation. If a participant withdrew from the study before completing all assessments or was deemed to meet any exclusion criteria after arriving at the first visit, he/she was determined to be ineligible for the full payment and was paid $5.

Imaging Acquisition and Analysis

Diffusion Tensor Imaging (DTI). Neuroimaging data were collected with a Siemens 3 Tesla MAGNETOM Trio high-speed scanning device at the Maryland Neuroimaging Center, equipped with a vendor-created 32-channel phase-array head coil. For structural purposes a T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE; Mugler & Brookeman, 1990) scan was collected with 208 sagittal slices, 0.8 mm slice thickness, 2400 ms TR, 2.01 ms TE, 8° flip angle, 0.8 mm in-plane voxel size, 240 mm x 256 mm FOV, 300 x 320 matrix. Additionally, two paired spin echoes with 3 volumes per spin echo and reversed phase encoding (AP and PA) of 208 sagittal slices with 1.63 mm slice thickness, 9460 ms TR, 58 ms TE, 90° flip angle, 2.17 mm in-plane voxel size, 208 mm x 208 mm FOV, 96 x 96 matrix were collected to create the fieldmaps. Of note, due to operator error, the first 15 participants who completed the scanning protocol did not have the AP/PA spin echoes rotated, thus the same direction was collected twice. A comparison between the group with rotated spin echoes and the group without rotated spin echoes on demographic and behavioral outcome variables yielded no significant differences. High-angular resolution diffusion-weighted images were collected using a single-shot, spin-echo echo-planar imaging sequence with 257 isotropically distributed diffusion weighted directions with b = 1,000 s/mm^2 and two diffusion un-weighted (b = 0) images. The acquisition parameters were as follows: 90 axial slices with 1.63 mm slice thickness, 4000 ms TR, 94 ms TE, 78° flip angle, 1.625 in-plane voxel size, 208 mm x 208 mm FOV, 128 x 128 matrix, total scan time: 18 minutes. Of note, other images not described above were collected as part of this study; however, they were not required for these analyses and thus will not be reported here.

Pre-processing of the imaging data was performed using the FSL 5.0.10 (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl). First, fieldmaps were created through topup. Then it was corrected for eddy-currents and head motion through affine registration using eddy_openmp. Next, brain-extraction was undertaken using the Brain Extraction Tool (BET, part of FSL). FA images were calculated using DTIFit, which fits a diffusion tensor model at each voxel. A group map was created using Tract-Based Spatial Statistics (TBSS; Smith et al., 2004) by first removing brain-edge artifacts and likely outliers from the diffusion tensor imaging. Second, all FA images were aligned to 1 mm standard space using nonlinear registration to FMRIB58_FA template. Next, the mean FA image was created and thinned to create a mean FA skeleton which represented the centers of all common tracts to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data were fed into voxel-wise statistics.

Regions of interest (ROIs) were defined in the inferior longitudinal fasciculus (ILF) and the uncinate fasciculus (UF). Regions were created by overlying the TBSS-generated skeleton with the Johns Hopkins University DTI-based White Matter Atlas (http://cmrm.med.jhmi.edu) (Mori, Wakana, Nagae-Petscher, & van Zijl, 2005; Wakana et al., 2004) for the tracts of interest. Voxel-wise simple regression analyses of behavioral variables predicting FA were performed using Statistical Parametric Mapping version 12 (SPM12) as part of MATLAB (http://www.mathworks.com) version R2017a. These imaging analyses were conducted using a voxelwise threshold of $p = 0.001$, $p = .05$ cluster extent threshold corrected for family wise error rate both within the masks and the whole brain. Additionally, Pearson correlations between behavioral variables and the average FA value within each tract per hemisphere were conducted using SPSS 24.0. Age, gender, education, and smoking status were included in the analyses as confounding regressors.

Data Analysis

We conducted analyses in several stages. First, we pre-processed the neuroimaging data to correct for artifacts, noise, and movements, as described above. Next, we conducted an outlier analysis for behavioral and imaging variables. We then examined the psychometric properties and intercorrelations between our variables of interest, including the BLERT, Hinting Task, B-CATS, CAINS, and SLOF. Next, we conducted analyses to assess the relation between white matter integrity within the UF and ILF and measures of social cognition for Aim 1. Then we examined the association between white matter integrity and social functioning for Aim 2. Finally, we conducted our Exploratory Aims: examining the contribution of general cognitive ability to white matter integrity within the UF and ILF, and a whole brain approach to identify possible other white matter tracts involved in theory of mind and emotion processing. These analyses are described below. Behavioral data were analyzed with SPSS 24.0 and neuroimaging data were analyzed with SPM12 and SPSS 24.0.

Preliminary Aim 1. To assess the psychometric properties of our primary variables of interest, we examined the internal consistency of the Hinting Task, the BLERT, and the SLOF. Next, we ran correlations to determine the associations between social cognition, social functioning, negative symptoms, and general cognitive ability.

Aim 1. To address our hypothesis that white matter microstructure as measured through FA values within the UF and ILF tracts will be positively correlated with social cognitive ability, we conducted simple regressions between the FA values with measures of theory of mind (the Hinting Task) and emotion processing (the BLERT) and Pearson correlations between the average FA value for each tract per hemisphere with social cognition tasks.

Aim 2. To address our hypothesis that white matter microstructure as measured through FA values within the UF and ILF tracts will be positively correlated with real-world functioning, we conducted simple regressions between the FA values with social functioning (SLOF) and Pearson correlations between the average FA value for each tract per hemisphere with the SLOF.

Exploratory Aim 1. To address whether the ILF and UF tracts are specific to social cognition and not general cognition, we planned to conduct a multiple regression to examine the contribution of cognitive ability (B-CATS) and social cognition (BLERT and Hinting Task) to FA values within the UF and ILF tracts.

Exploratory Aim 2. To address other possible cerebral white matter networks involved in social cognition, we employed a whole brain analysis approach. To examine FA across the entire skeleton, we conducted a non-parametric permutation analysis using the ‘randomize’ tool in FSL. We performed 10,000 permutations using the Threshold Free Cluster Environment, which is a rigorous method that identifies clusters in the data without having to predefine the clusters (Smith & Nichols, 2009).

Chapter 3: Results

Sample Characteristics

Demographic information can be found in table one. Clinical interview and behavioral measure ratings are described in table two, and mean FA values within tracts of interest are listed in table three. Independent t-tests and chi-square analyses yielded no significant differences in age, gender, or race; however, the clinical group reported significantly fewer years of education.

Table 1. Demographic Data

	Patients (n = 25)	**Controls** (n = 8)	**Statistic**	***p*-value**
Diagnosis				
Schizophrenia	14	--	--	--
Schizoaffective Bipolar	5	--		
Schizoaffective Depressed	2	--		
Bipolar I w/ psychotic features	4	--		
Age				
M (SD)	45.3 (11.2)	48 (10.4)	$t(31) = 0.61$	.547
Gender			$\chi^2(1) = 0.33$	.566
Male	16	6		
Female	9	2		
Race			$\chi^2(2) = 0.49$	.783
Black	21	7		
White	3	1		
Asian	1	0		
Education				
Years, *M (SD)*	11.2 (1.8)	12.9 (2.6)	$t(31)= 2.13$	.042

Regarding clinical symptoms, the combined sample reported low levels of psychiatric symptoms on the BPRS (a score of 1 = not present), mild to moderate levels of experiential negative symptoms on the CAINS MAP, and mild levels of expressive negative symptoms on the CAINS EXP (a score of 1 = mild; 2 = moderate). Additionally, the combined sample evidenced average estimated intelligence ($\bar{x}$ = 95), mild cognitive impairment (approximately one standard deviation below the norm), average theory of mind skills ($\bar{x}$ = 15.8; total possible = 20), poor emotion recognition skills ($\bar{x}$ = 11.9; total possible = 21), and moderate to high social, community, and overall functioning. Lastly, mean FA values within the tracts of interest (ILF and UF) were low.

Table 2. Clinical Interview & Behavioral Measures Data

	Participants (*n* = 33)	
	M (*SD*)	Range
CAINS		
MAP	13.8 (6.5)	3 – 29
EXP	5.7 (4.1)	0 – 14
BPRS		
Total	34.6 (10.5)	24 – 77
Positive	1.4 (0.5)	1 – 3.25
Negative	2.0 (1.0)	1 – 4.33
Agitation-Mania	1.2 (0.3)	1 – 2
Depression-Anxiety	1.7 (0.8)	1 – 4.25
WTAR		
Estimated Full Scale IQ	95.2 (13.2)	70 – 118
B-CATS		
Digit Symbol (scaled sore)	6.4 (2.8)	3 – 14
Category Fluency	42.9 (10.9)	22 – 66
Trail Making B (seconds)	133.9 (63.1)	32 – 300
Composite (*z*-score)	-0.9 (0.9)	-2.3 – 1.0
SLOF		
Social	53.3 (8.0)	24 – 65
Community	78.7 (7.9)	55 – 85
Total	132 (12.0)	98 – 149
BLERT	11.9 (3.8)	4 – 19
Hinting Task	15.8 (3.9)	5 – 20

CAINS = Clinical Assessment Interview for Negative Symptoms; MAP = Motivation and Pleasure; EXP = Expression; BPRS = Brief Psychiatric Rating Scale; WTAR = Wechsler

Test of Adult Reading; B-CATS = Brief Cognitive Assessment Tool for Schizophrenia; SLOF = Specific Levels of Functioning; BLERT = Bell Lysaker Emotion Recognition Task

Table 3. Fractional Anisotropy Values within Tracts of Interest

	Participants (*n* = 33)	
	M (*SD*)	Range
Right UF	.103 (.008)	.086 – .117
Left UF	.101 (.008)	.089 – .117
Right ILF	.160 (.008)	.138 – .185
Left UF	.124 (.008)	.105 – .143

UF = Uncinate Fasciculus; ILF = Inferior Longitudinal Fasciculus

Behavioral Data

Outlier analyses yielded one outlier for the SLOF Social and one outlier for the SLOF Community; there were no outliers with regard to the Hinting Task, BLERT, B-CATS, or SLOF Total. The following results were unchanged when outliers were removed from the data. An examination of the primary outcome variables' psychometric properties indicated good internal consistency for the Hinting Task (α = .81), SLOF Social (α = .85), SLOF Community (α = .87), and SLOF Total (α = .87); however, Cronbach's alpha for the BLERT (α = .53) suggested poor internal consistency. To assess the relations between social cognition, general cognitive ability, negative symptoms, and functioning, we computed correlations between the BLERT, Hinting Task, B-CATS, CAINS, and SLOF (see table 4). Consistent with prior research, social cognition, as measured by the BLERT and the Hinting Task, was positively correlated with general cognitive ability. However, contrary to prior work, neither social cognition measure was significantly correlated with overall psychosocial functioning (SLOF Total) or social functioning (SLOF Social). Theory of mind (Hinting Task), but not emotion processing (BLERT), was positively correlated with community functioning (SLOF Community). Similarly, only the Hinting Task was related to expressive negative symptoms (CAINS EXP) with greater expressive negative symptoms associated with poorer theory of mind skills; neither social cognition measure was correlated with experiential negative symptoms (CAINS MAP). Regarding the relation between negative symptoms and functioning, greater experiential negative symptoms were related to lower social functioning. There were no other significant associations between negative symptoms and SLOF subscales. Lastly, poorer cognitive ability was related to higher experiential and expressive negative symptoms.

Table 4. Correlations Between Social Cognition, General Cognitive Ability, Negative Symptoms, and Functioning

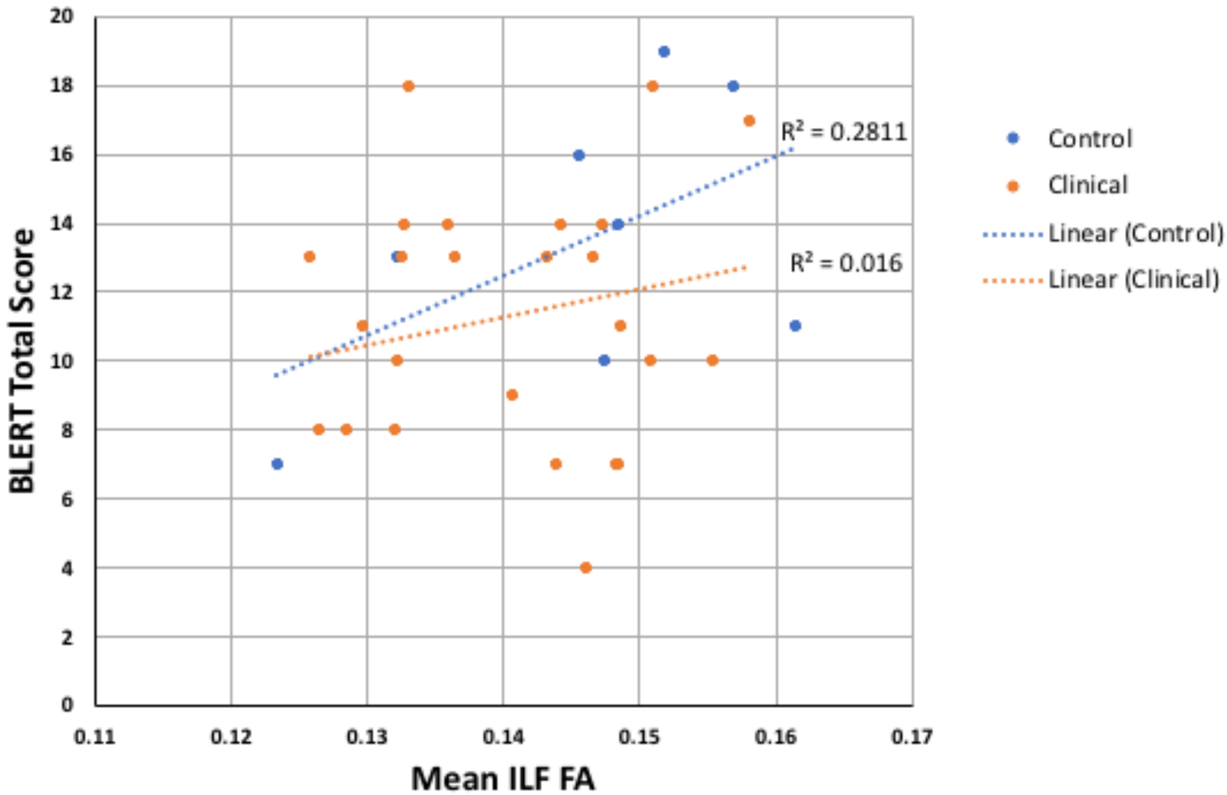
	1	2	3	4	5	6	7	8
1. BLERT	--							
2. Hinting Task	.526**	--						
3. B-CATS	.428*	.436*	--					
4. CAINS MAP	-.276	-.166	-.352*	--				
5. CAINS EXP	-.288	-.454**	.490**	.501**	--			
6. SLOF Soc.	-.227	-.017	.014	-.473**	-.319^	--		
7. SLOF Comm.	.185	.468**	.305^	.042	-.131	.148	--	
8. SLOF Total	-.029	.296^	.210	-.286	-.298^	.761**	.754**	--

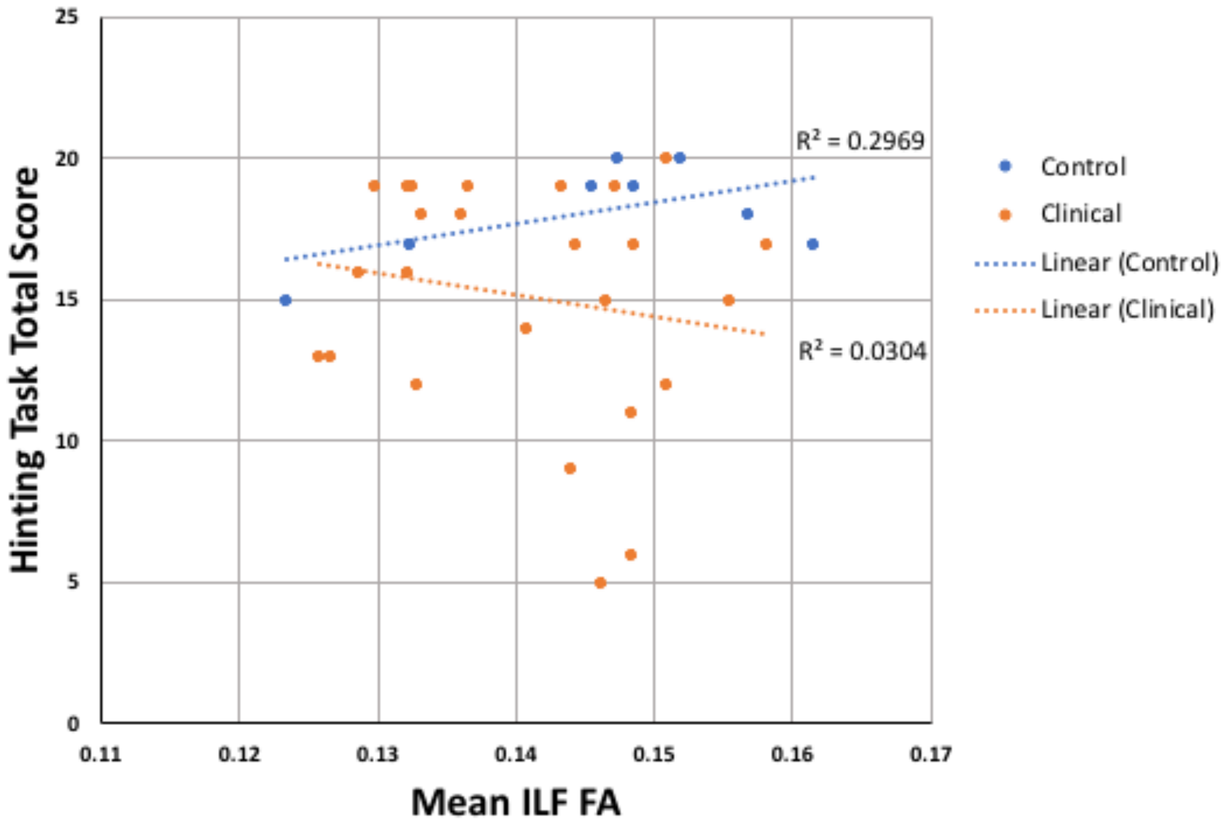
** $p < .01$; * $p < .05$; ^ $p < .10$; CAINS = Clinical Assessment Interview for Negative Symptoms; MAP = Motivation and Pleasure; EXP = Expression; B-CATS = Brief Cognitive Assessment Tool for Schizophrenia; BLERT = Bell Lysaker Emotion Recognition Task; SLOF = Specific Levels of Functioning

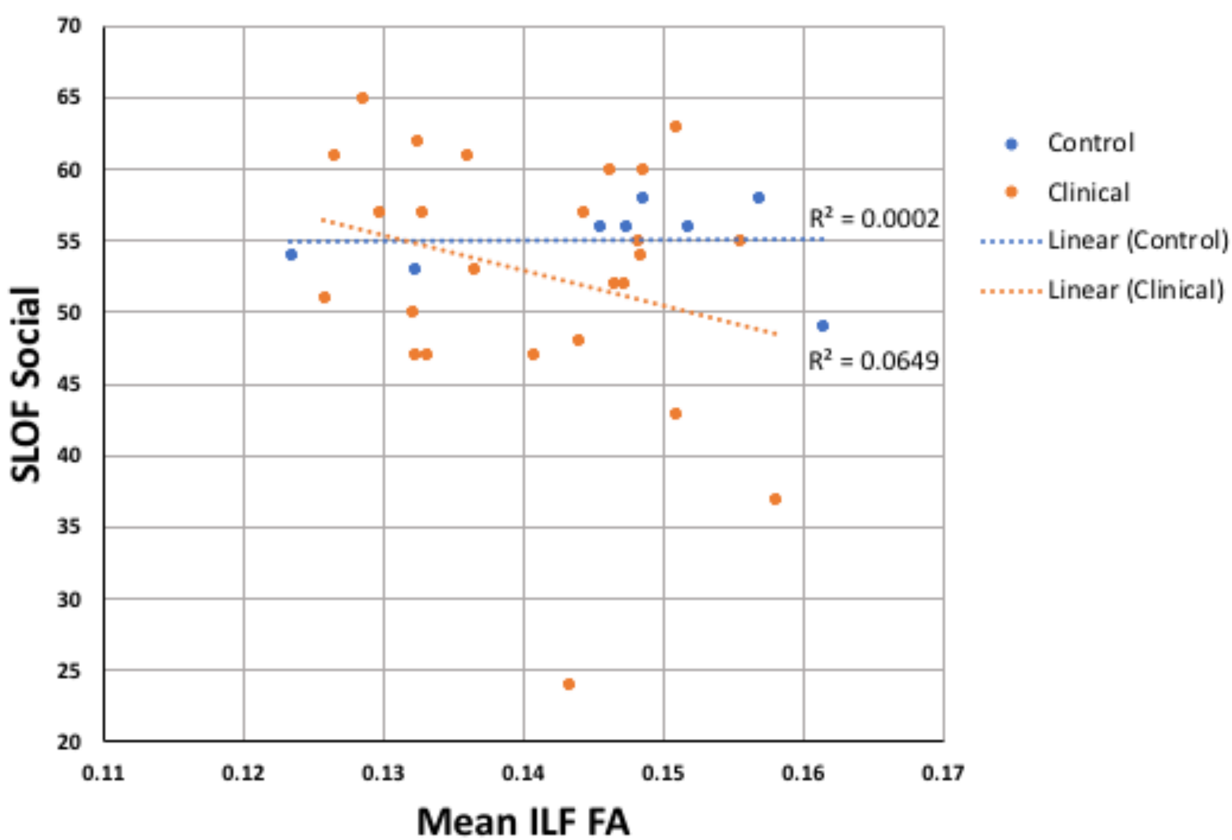
Neuroimaging Data

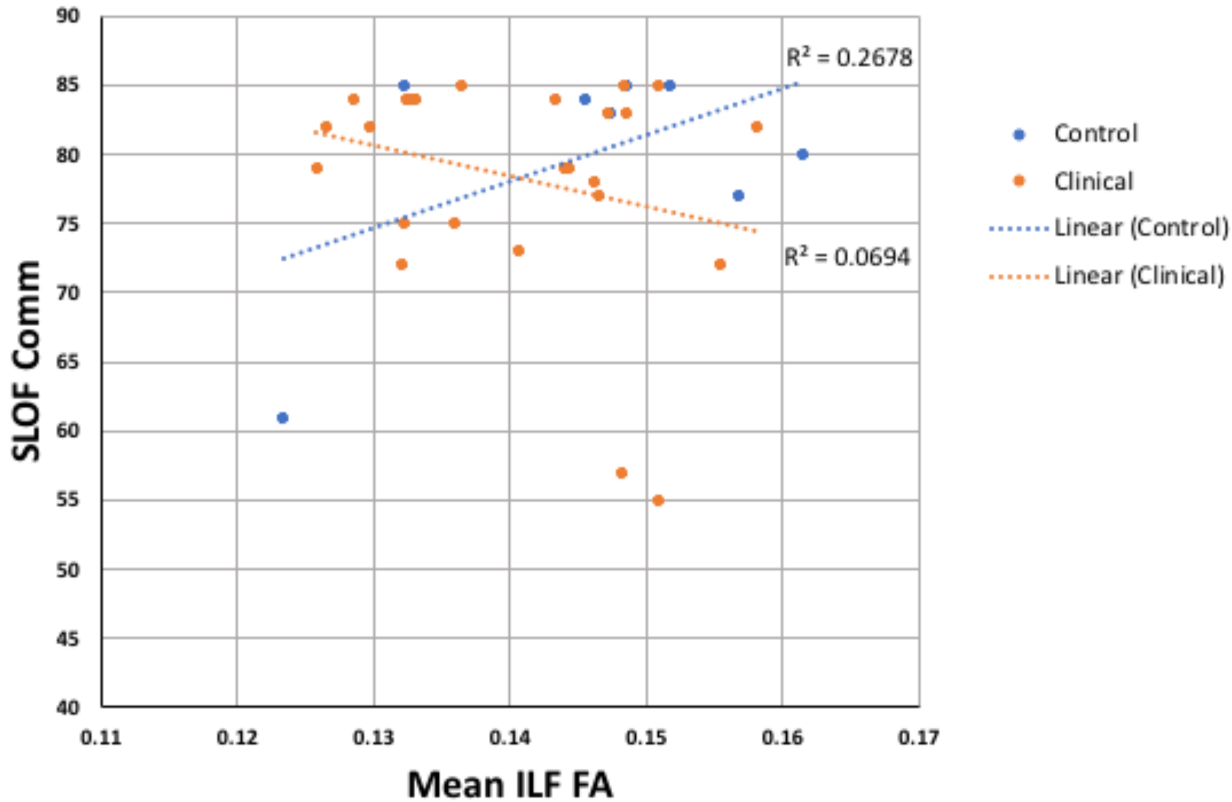
Primary Aims. Outlier analyses indicated no outliers for average FA values within the ILF or the UF. Scatterplots of the relationship between each behavioral variable and mean FA value of the ILF and UF collapsed across hemispheres are presented in Figures 1 and 2, respectively. Partial correlations (controlling for age, gender, education, and smoking status) between average FA values among the right and left ILF and UF tracts with social cognition and social functioning measures are presented in table 5. In regard to aim 1, neither social cognition measure (BLERT or Hinting Task) was correlated with FA values in the ILF or the UF (all p's $> .001$). Regarding aim 2, there was a significant relation between FA values in the left inferior longitudinal fasciculus with overall psychosocial functioning (SLOF Total) ($k = 13$, $t = 4.02$, $p < .001$, peak location = -41, -41, 8; $pr = -.43$, $p < .05$) and social functioning ($pr = -.46$, $p < .05$), and FA values in the left uncinate fasciculus with community functioning ($pr = -.34$, $p < .05$). However, the direction of these relations were not as we predicted as higher FA in these tracts was associated with *poorer* functioning.

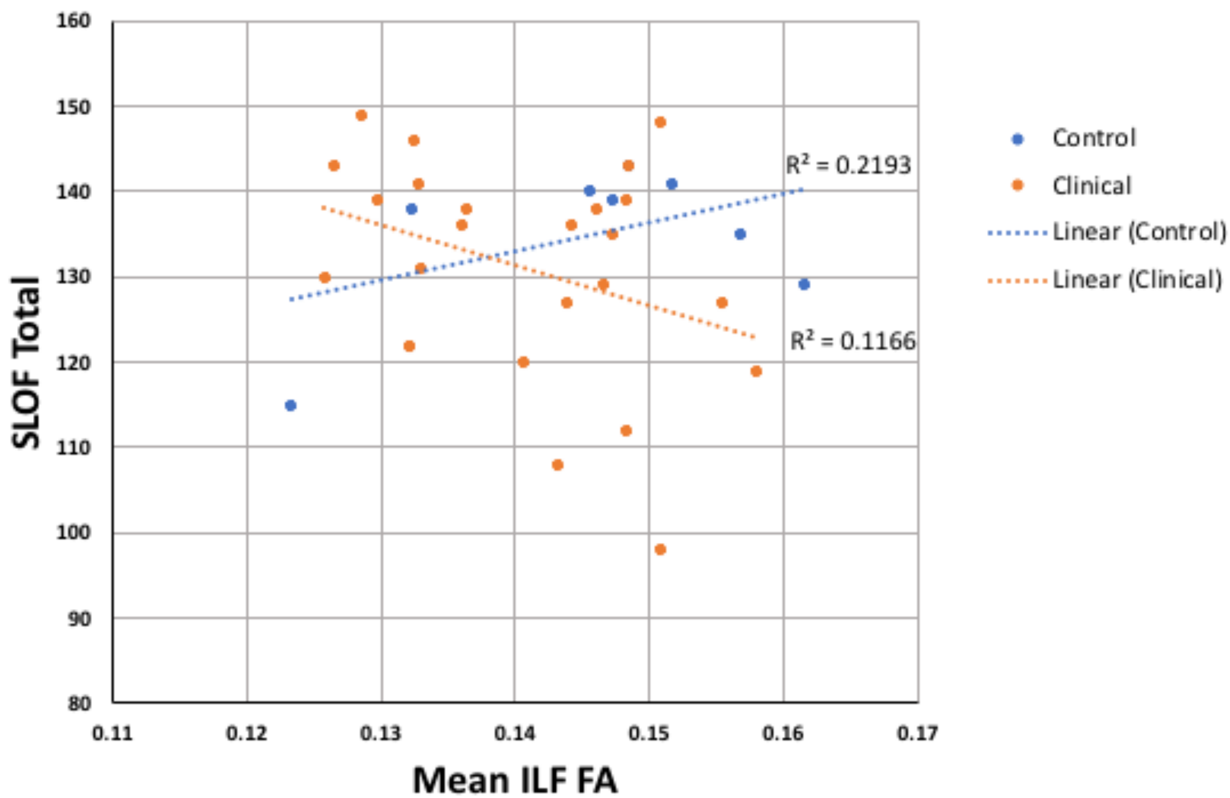
Figure 1. Relationships Between Mean Inferior Longitudinal Fasciculus Fractional Anisotropy with Social Cognition and Functioning as a Function of Group

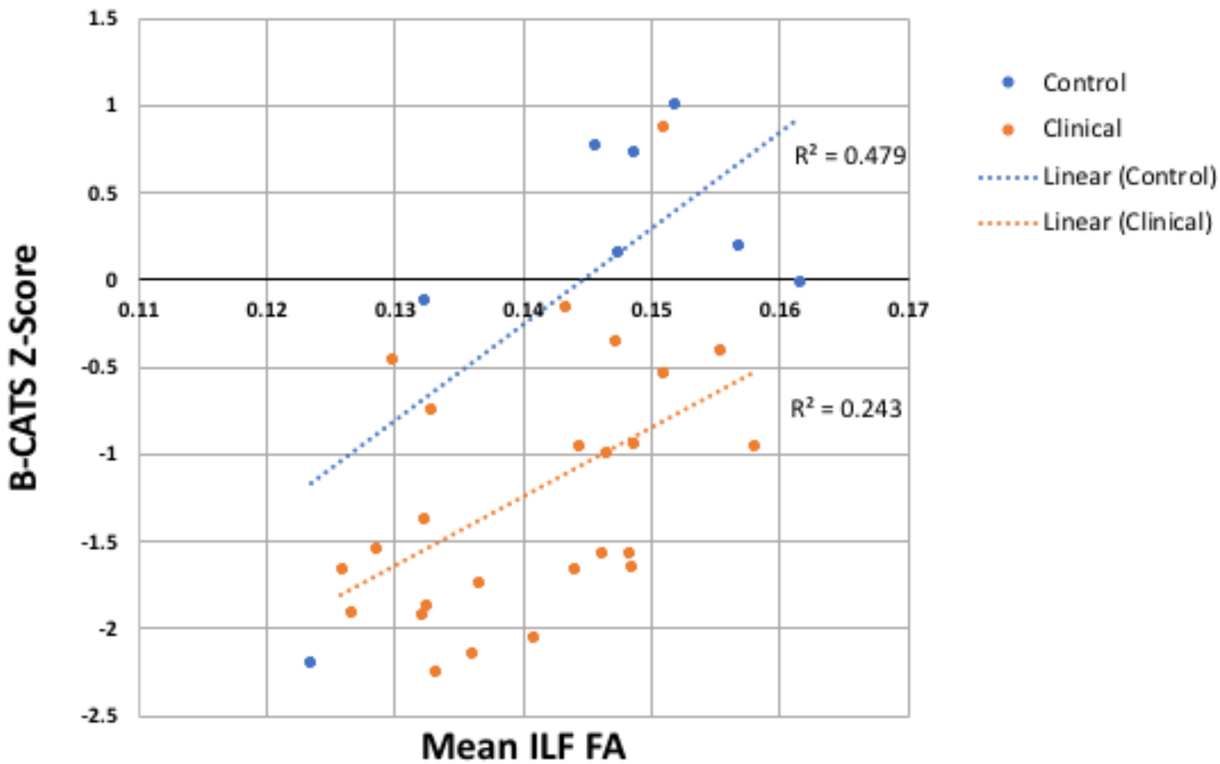



Hinting Task Total Score
Mean ILF FA
0
5
10
15
20
25
0.11
0.12
0.13
0.14
0.15
0.16
0.17
$R^2 = 0.2969$
$R^2 = 0.0304$
Control
Clinical
Linear (Control)
Linear (Clinical)


SLOF Social
Mean ILF FA
20
25
30
35
40
45
50
55
60
65
70
0.11
0.12
0.13
0.14
0.15
0.16
0.17
$R^2 = 0.0002$
$R^2 = 0.0649$
Control
Clinical
Linear (Control)
Linear (Clinical)

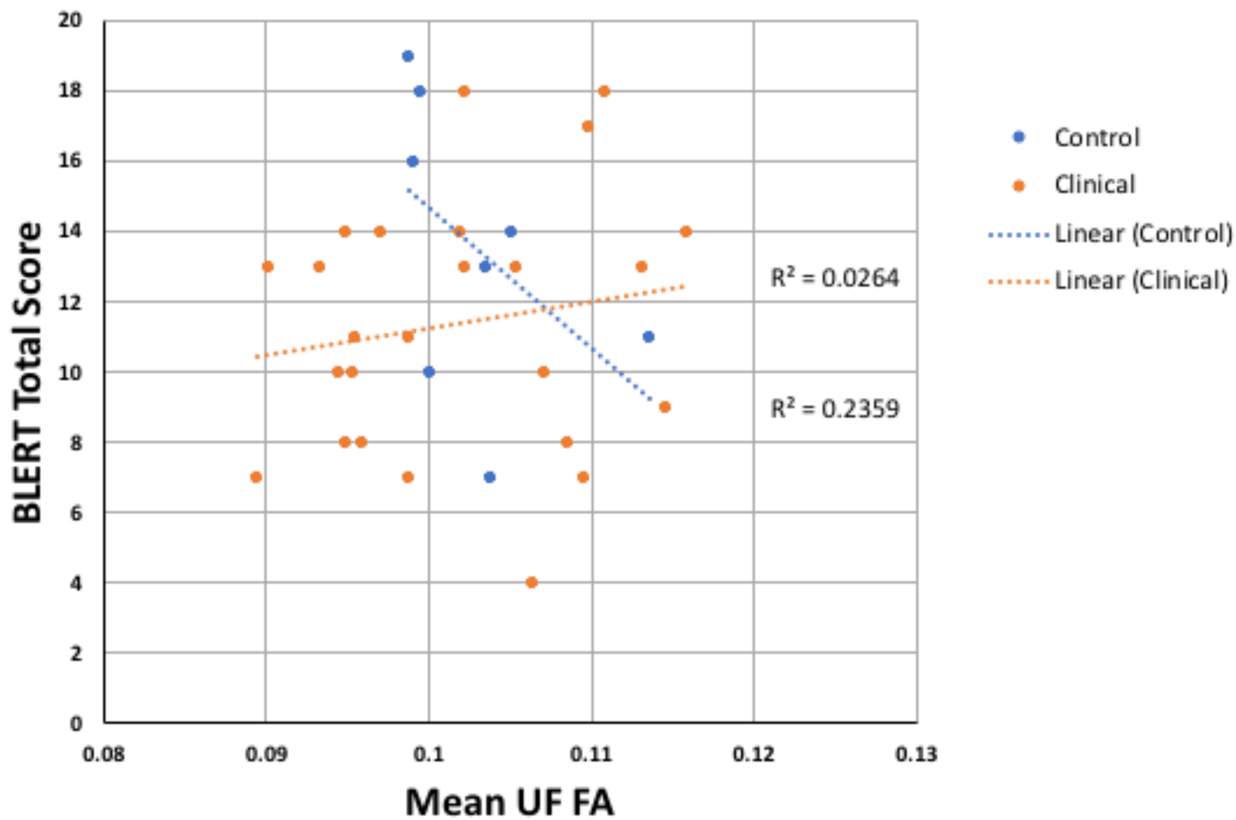

90
85
80
75
70
65
60
55
50
45
40
SLOF Comm
0.11
0.12
0.13
0.14
0.15
0.16
0.17
Mean ILF FA
R² = 0.2678
R² = 0.0694
Control
Clinical
Linear (Control)
Linear (Clinical)

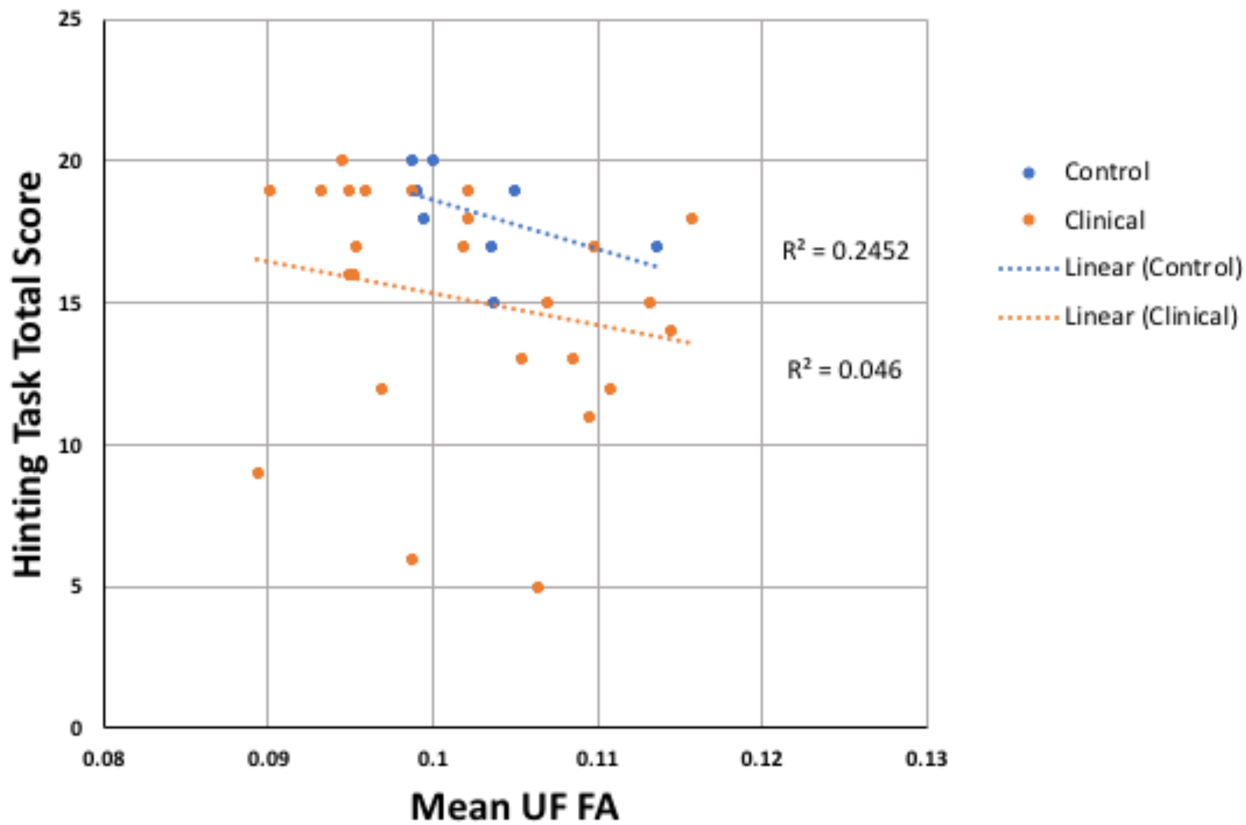

160
150
140
130
120
110
100
90
80
SLOF Total
0.11
0.12
0.13
0.14
0.15
0.16
0.17
Mean ILF FA
R² = 0.2193
R² = 0.1166
Control
Clinical
Linear (Control)
Linear (Clinical)

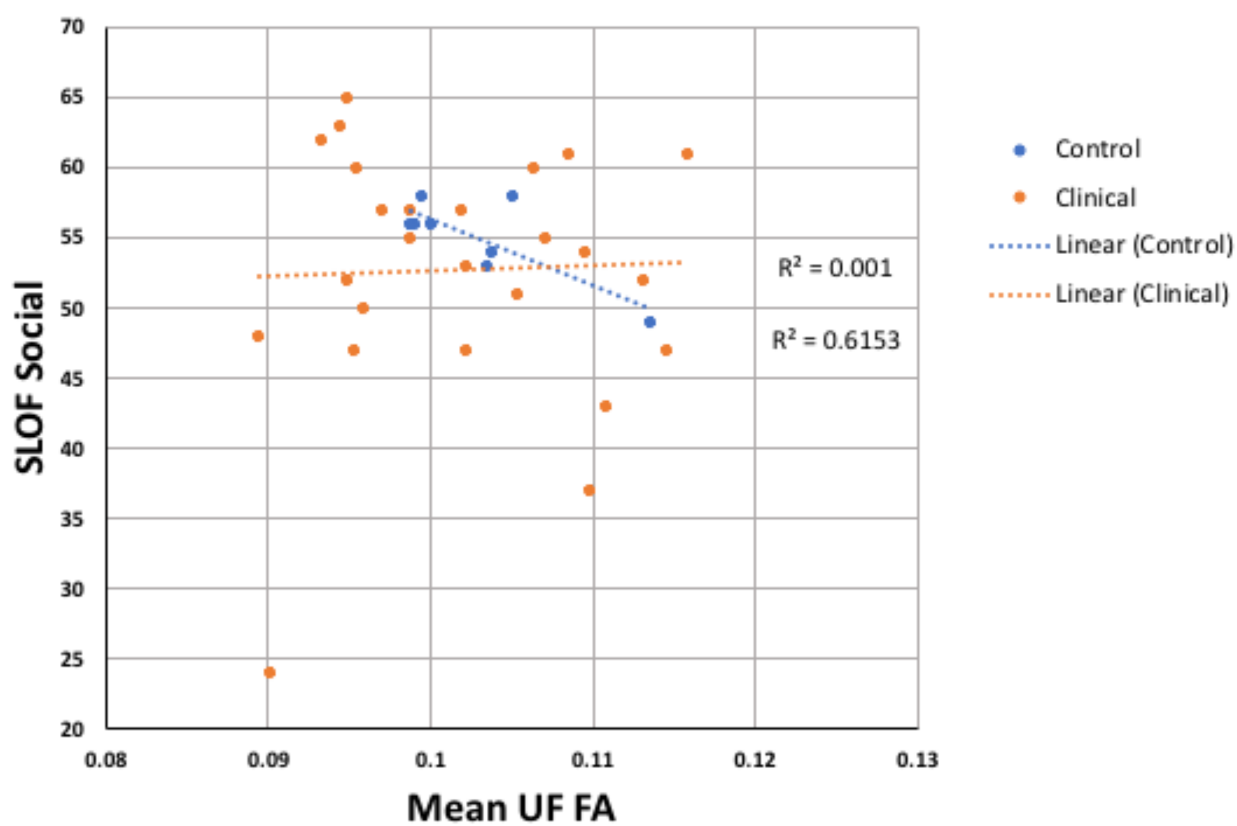


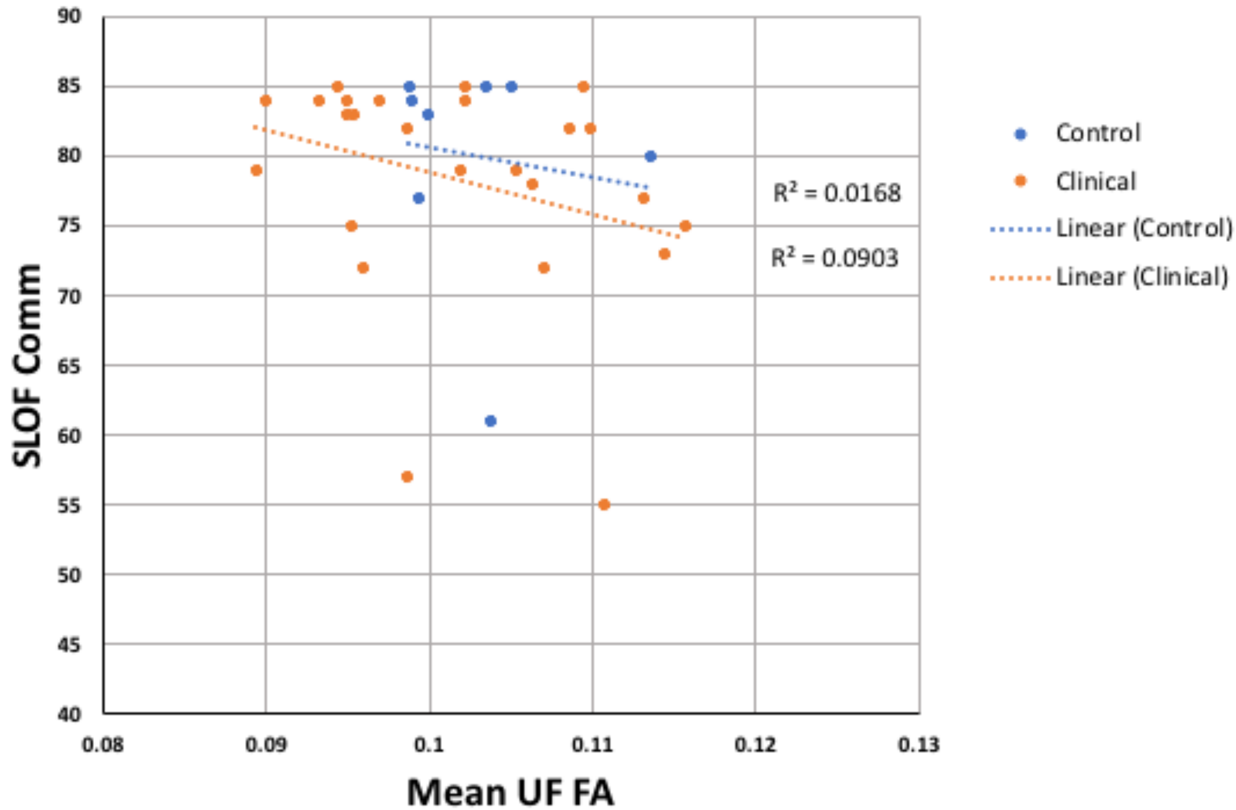
B-CATS Z-Score
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
0.11
0.12
0.13
0.14
0.15
0.16
0.17
Mean ILF FA
R² = 0.479
R² = 0.243
Control
Clinical
Linear (Control)
Linear (Clinical)

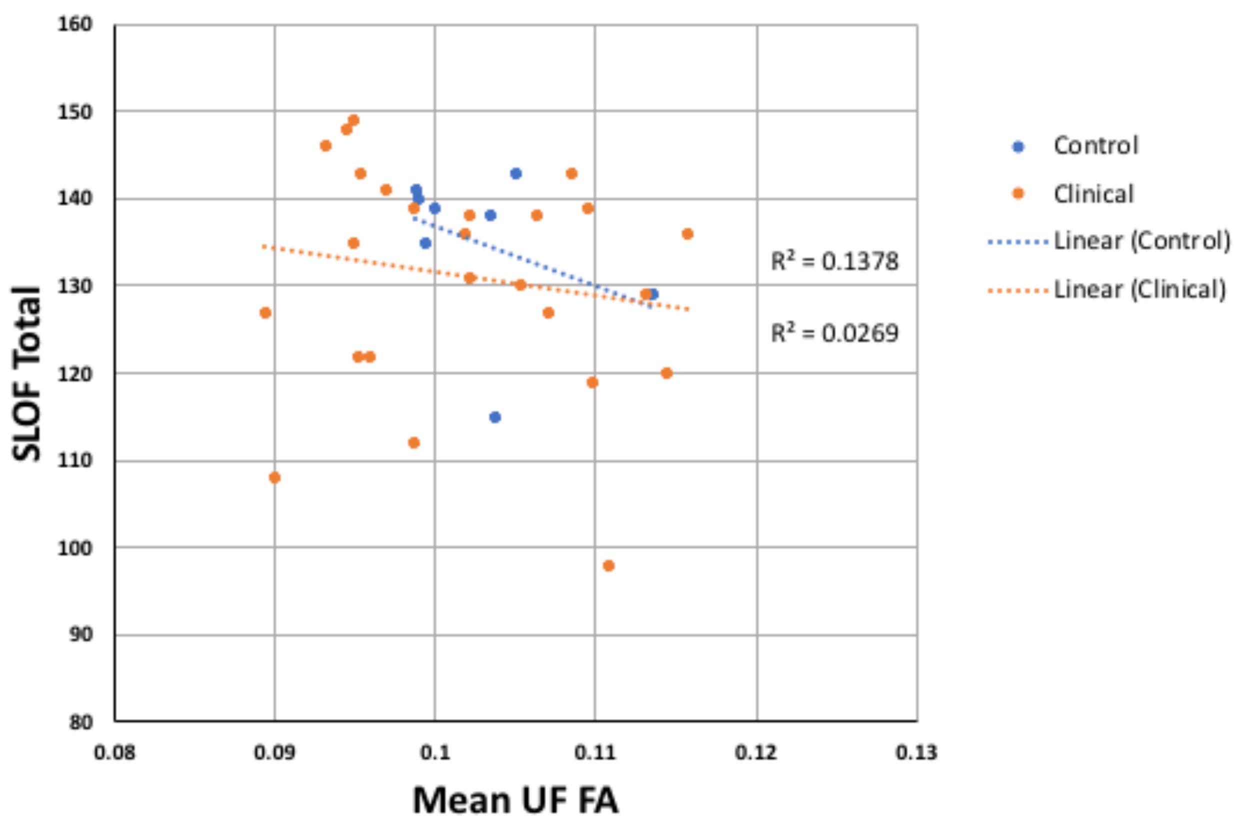
Figure 2. Relationships Between Mean Uncinate Fasciculus Fractional Anisotropy with Social Cognition and Functioning as a Function of Group

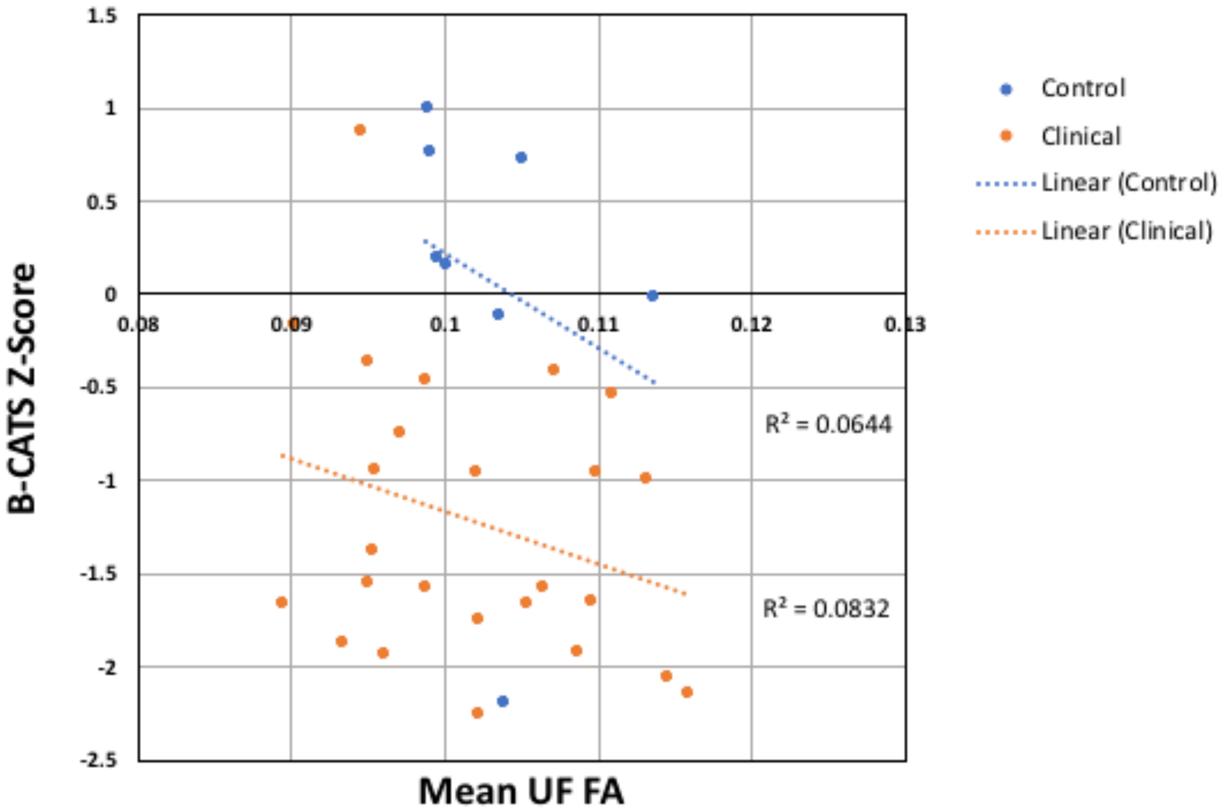



25
20
15
10
5
0
0.08
0.09
0.1
0.11
0.12
0.13
Hinting Task Total Score
Mean UF FA
R² = 0.2452
R² = 0.046
Control
Clinical
Linear (Control)
Linear (Clinical)


70
65
60
55
50
45
40
35
30
25
20
0.08
0.09
0.1
0.11
0.12
0.13
SLOF Social
Mean UF FA
R² = 0.001
R² = 0.6153
Control
Clinical
Linear (Control)
Linear (Clinical)


90
85
80
75
70
65
60
55
50
45
40
SLOF Comm
0.08
0.09
0.1
0.11
0.12
0.13
Mean UF FA
R² = 0.0168
R² = 0.0903
Control
Clinical
Linear (Control)
Linear (Clinical)


160
150
140
130
120
110
100
90
80
SLOF Total
0.08
0.09
0.1
0.11
0.12
0.13
Mean UF FA
R² = 0.1378
R² = 0.0269
Control
Clinical
Linear (Control)
Linear (Clinical)



B-CATS Z-Score
Mean UF FA
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
0.08
0.09
0.1
0.11
0.12
0.13
Control
Clinical
Linear (Control)
Linear (Clinical)
R² = 0.0644
R² = 0.0832

Table 5. Partial Correlations Between Fractional Anisotropy Values with Tracts of Interest, Social Cognition, and Functioning

	BLERT	**Hinting Task**	**SLOF Social**	**SLOF Comm**	**SLOF Total**
Right UF	.070	-.263	.167	-.207	-.029
Left UF	.092	.020	-.010	-.335*	-.223
Right ILF	-.117	-.303	-.262	-.202	-.294
Left ILF	.076	-.066	-.457*	-.227	-.431*

* $p < .05$; UF = Uncinate Fasciculus; ILF = Inferior Longitudinal Fasciculus; BLERT = Bell Lysaker Emotion Recognition Task; SLOF = Specific Levels of Functioning

Exploratory Aims. Given that there were no significant associations between social cognition scores and FA within tracts of interest, we did not conduct a multiple regression to examine the contribution of cognitive ability (B-CATS). Regardless, a simple regression yielded no significant correlations between general cognitive ability and FA values in either the ILF or the UF. Similarly, the whole brain analysis examining potential alternative tracts implicated in social cognition and social functioning did not identify any white matter tracts with significant correlations between FA value and scores on the BLERT, Hinting Task, or SLOF.

Chapter 4: Discussion

In this study we sought to examine the contribution of white matter integrity to social cognitive ability and social functioning among individuals with and without clinically significant psychotic symptoms. An additional aim was to examine the associations between social cognitive ability, social functioning, negative symptoms, and general cognitive ability. Although social cognition and white matter microstructure has been well-studied in schizophrenia samples, this study extended upon prior work through employing an RDoC approach (Insel, et al., 2010). Specifically, we recruited both healthy controls and a transdiagnostic sample including clinical participants diagnosed with schizophrenia spectrum disorders as well as those diagnosed with mood disorders with psychotic features and then combined all participants into one sample for analyses in the service of examining social cognitive abilities ranging along a dimensional continuum from healthy to pathological. Further, we examined social cognition and social functioning across three RDoC units of analysis, including circuits, paradigms, and self-report.

Our first hypothesis regarding the relations between social cognition, functioning, negative symptoms, and general cognition was partially supported. Higher negative symptoms were related to poorer cognitive functioning. Overall, this finding is in line with prior research which suggests a modest relationship (*r*s generally ranging from .20 to .30) between both negative symptom facets and cognitive ability among individuals with schizophrenia (Blanchard et al., 2017; for a review, see Harvey, Koren, Reichenberg, & Bowie, 2006). However, other researchers have failed to find such a relation (Kring, Gur, Blanchard, Horan, & Reise, 2013) and it has been suggested that negative symptoms and cognitive ability are separable domains in schizophrenia spectrum disorders (Harvey, et al., 2006). The specific relation between CAINS EXP and the B-CATS in our study was more robust than is typically cited in the literature, and this may be a result of our mixed sample.

Expressive, but not experiential, negative symptoms were related to theory of mind ability. Negative symptoms have been consistently shown to contribute to poorer theory of mind skills (Corcoran et al., 1995; Couture, Granholm, & Fish, 2011). Researchers who have examined the differential association between the two negative symptom domains and theory of mind have found that only expressivity symptoms are significantly negatively correlated with scores on the Hinting Task (Bell, Corbera, Johannesen, Fiszdon, & Wexler, 2011). Bell and colleagues also failed to find a relation between either negative symptom domain and emotion processing. Research from the developmental literature demonstrates that theory of mind skills contribute to emotion knowledge, which includes the ability to identify emotion expressions and understand the motivational function of emotions (Seidenfeld, Johnson, Woodburn Cavadel, & Izard, 2014), and this was evidenced within our adult sample as the BLERT and Hinting Task were correlated in this study. One can speculate that individuals who do not display many facial expressions may not fully understand the motivational function of emotions and thus this impacts their ability to understand that others may have different thoughts and feelings than their own. This is at least partially supported by recent work showing that individuals with schizophrenia report similar levels of willingness to engage in future interactions with an affiliative person as healthy controls despite displaying poorer verbal, nonverbal, and affiliative skills during a role play (Blanchard, Park, Catalano, &

Bennett, 2015). Therefore, although they are motivated to engage with another person, they may be unaware that their decreased emotional expression may negatively impact the likelihood that another person would want to interact with them.

In line with prior research, general cognitive ability was moderately correlated with social cognition, highlighting that although they are related, they are indeed distinct constructs (Sergi et al., 2007). A recent systematic review of factor analytic studies demonstrated that six of nine studies found social cognition and general cognitive ability to be distinct factors and that the shared variance between these two domains generally ranges between 39-77% among individuals with schizophrenia (Mehta et al., 2013). Social cognition has also been found to be distinct from general cognition among healthy samples (Allen & Barchard, 2009).

We observed a significant, moderate association between experiential negative symptoms and social functioning and trend level relationships between expressive negative symptoms and social and overall functioning. This adds to the growing body of literature that negative symptoms contribute to real-world functioning and social impairment (Blanchard et al., 2017; Rocca et al., 2014). Further, the results from this mixed transdiagnostic sample are consistent with prior findings of a differential relationship such that experiential negative symptoms (CAINS MAP) have a more robust connection to functional impairment than expressive negative symptoms (CAINS EXP) within individuals with schizophrenia (Blanchard et al., 2017).

Theory of mind was differentially related to functioning as better theory of mind skills were associated with enhanced community functioning, though not social or overall functioning. However, there was a trend level positive relation between theory of mind and overall functioning, and the magnitude of this correlation was greater than that of the correlation between the Hinting Task and SLOF total reported in the SCOPE study (r = .296 vs. r = .197; Pinkham, Penn, Green, & Harvey, 2016). It is likely that we were simply underpowered to detect this effect. Although we expected that better theory of mind skills would be related to improved social functioning, our null finding is in line with prior work with ultra-high risk samples, which has found that the Hinting Task was not related to functioning, and another theory of mind measure (the Visual Jokes Task) was significantly associated with global and role functioning, though not social functioning (Cotter et al., 2017).

It is surprising that emotion processing was not related to negative symptoms or functioning. Possibly contributing to these null findings is that in our sample the BLERT task evidenced poor internal consistency and participants averaged low total scores on this task. Poor internal consistency was observed in our combined sample and also in both the clinical (α = .599) and control participants (α = .498). The SCOPE study reported acceptable internal consistency of the BLERT in their clinical sample (α = .737), but marginally poor internal consistency in their control sample (α = .626). Our controls did not evidence a truncated range of scores on this assessment (range = 10 – 19), thus it is unclear what may be contributing to the poor internal consistency within our sample. Future examination of performance on the BLERT within healthy samples may be warranted. Average BLERT scores tend to range from 13 to 14 within schizophrenia samples and 15 to 17 within healthy controls (Kalin et al., 2015; Pinkham, Penn, Green, & Harvey, 2016); however, our combined sample had an average total score of 11.9. Given that our sample was primarily Black and the actor in the BLERT videos is White, the low scores in our sample may be attributable to the other-race effect, which suggests that individuals are better at recognizing and distinguishing same-race faces than other-race faces (Gross, 2009). Pinkham and colleagues (2017) recently examined the effect of race, age, and sex on social cognitive performance among individuals with schizophrenia and found a large effect of participant race on BLERT performance but not on emotion processing assessments with racially diverse stimuli. The authors additionally found an effect of age on BLERT performance such that older adults had poorer task performance. Prior research examining the effect of age on facial expression recognition among healthy individuals is in line with Pinkham's findings, though demonstrates a more nuanced perspective. In comparison to younger adults, older adults exhibit reduced expression of and ability to identify negative (i.e., sadness, anger, fear), but not positive, facial emotions (Calder et al., 2003; Keightley, Chiew, Wincour, & Grady, 2007). Given that the mean age of our participants was 45, age may have also contributed to the observed emotion perception impairment.

The results from the neuroimaging data analyses failed to find the predicted contribution of white matter integrity among the ILF and UF to social cognition and social functioning. However, the results revealed that greater structural integrity in the left ILF as measured by FA was related to poorer overall and social functioning and that greater structural integrity in the left UF was related to poorer community functioning.The lateralization on the left side is consistent with prior work (Krakauer et al., 2017). Surprisingly, the direction of these brain-behavior relationships was unexpected as lower FA values within the ILF and UF are typically associated with poorer functioning (Karlsgodt, Niendam, Bearden, & Cannon, 2009; Krakauer et al., 2017). Given that this result was unanticipated per our a priori hypothesis and comes in the context of a low powered study with an older, heterogeneous sample, further replication is required before drawing firm conclusions.

There are several reasons we may have observed null findings for our neuroimaging hypotheses. First, FA may not be the best metric of white matter microstructure among individuals with psychotic disorders. Although white matter integrity is traditionally measured using FA values, a novel permeability-diffusivity model (Sukstanskii, Yablonskiy, & Ackerman, 2004) addresses a limitation of the standard DTI-FA model, which assumes a single pool of anisotropically diffusing water. The permeability-diffusivity model suggests two pools of water that behave as a bi-exponential function of *b*-values and are caused by the presence of a permeable membrane (Clark, Hedehus, & Moseley, 2002; Wu et al., 2011). Within neural white matter, axonal membranes are considered to be semi-permeable via both passive exchange (diffusion) and active exchange through ionic and water pumps (Baslow, 2002). Permeability-diffusivity index (PDI) is the parameter derived from this model and is considered to be sensitive to axonal membrane permeability. Research examining FA values and PDI values within the corpus callosum across individuals with schizophrenia has found that the effect size of PDI measurements between groups was significantly more robust than traditional FA values, indicating that PDI may be a more sensitive measure of white matter integrity (Kochunov, Chiappelli, & Hong, 2013). The researchers also found that schizophrenia is associated with restricted permeability of axonal membranes. Furthermore, although white matter is immutable after formation by oligodendrocytes, permeability of axonal membranes may be amendable. Recent work has shown that nicotine-related changes in white matter integrity contribute to improvements in processing speed and axonal permeability (Kochunov et al., 2013); therefore, this particular aspect of white matter microstructure could become a target for future pharmacological and psychosocial intervention work.

Second, given our relatively small sample size, we were likely underpowered to detect significant effects. Initial power analyses conducted prior to beginning the study indicated that a sample of 50 would likely yield an appropriate sample size to detect significant effects; however, only 33 participants were included in the neuroimaging data analyses. Low power, whether due to small sample size, small effects, or both, increases the likelihood of Type II errors thus producing more false negatives and it may also exaggerate the magnitude of effect sizes, a phenomenon known as the "winner's curse" (Button et al., 2013; Ioannidis, 2009). It is possible that our study may have failed to detect an actual effect or that published neuroimaging studies to date which have examined the contribution of white matter microstructure to social cognition and functioning in psychotic or high-risk samples experienced the "winner's curse" as they have recruited relatively moderate sample sizes ranging from 50 to 80 (Jalbrzikowski et al., 2014; Karlsgodt, Niendam, Bearden, & Cannon, 2009; Miyata et al., 2010; Zhao et al., 2017).

Third, the older age of our sample may have contributed to the null neuroimaging findings as white matter degrades over the lifespan. Prior research on white matter integrity among psychosis and high-risk samples and matched controls has typically recruited much younger samples (i.e., mean ages ranging from 15 to 38). Age-related declines in white matter FA in normal healthy adults is linear from about age 20 years onward (Salat et al., 2005). Regarding white matter changes, histological studies have demonstrated that white matter degradation consists of decreases in myelin density and in the number of myelinated fibers (Marner, Nyengaard, Tang, & Pakkengerg, 2003; Meier-Ruge, Ulrich, Bruhlmann, & Meier, 1992) and that white matter degradation as we age is even more prominent than cortical changes (Ge et al., 2002). Although these declines are most prominent in the anterior portions of the brain, research also suggests linear age-related decline in FA values among frontotempororal areas (Yoon, Shim, Lee, Shon, & Yang, 2008), which includes the UF and ILF tracts. It may be that our aged healthy control participants evidenced low FA values in these tracts which could decrease the full sample variance.

Another possible contributor relates to the challenges associated with conducting a study conforming to RDoC guidelines. First, given the heterogeneous samples recruited and that one goal of RDoC is to determine whether there is any variance among domains attributable to diagnosis, much larger sample sizes than we recruited for this study are required. Second, researchers have raised concerns about the difficulties of examining and comparing more distal units in the matrix, namely that observations at one level (e.g., behavior) can have a multiplicity of determinants at adjacent levels (e.g., physiology), which continue to grow in complexity as they progress through the hierarchy (Patrick & Hajcak, 2016; Lilienfeld & Treadway, 2016). This suggests that there are likely numerous other factors contributing to social cognitive ability and social functioning aside from white matter integrity. Additionally, there could be important physiological moderators of the relation between white matter microstructure and our two constructs of interest. Third, combining clinical and nonclinical samples in analyses may make it more difficult to detect significant effects, especially when relations between variables are only found in clinical samples. For example, some researchers have found an association between measures of social cognition and white matter microstructure in their clinical sample but not in the healthy controls (Jalbrzkowski et al., 2014; Miyata et al., 2010). Lastly, Lilienfeld (2014) has highlighted that RDoC seems to neglect measurement error, specifically psychometric weaknesses in laboratory measures and test-retest reliability of neuroimaging data. In line with this, we observed poor internal consistency of the BLERT task in our sample. Reliability problems have been raised even among structural neuroimaging methods as Boekel and colleagues (2015) attempted to replicate 17 effects among five previously published structural brain behavior studies and found evidence in favor of the null hypothesis for 16 of the 17 effects. Moreover, research has shown that repeated DTI scanning of the same individual in the same scanner on two separate occasions can yield variability in FA values, which can be related to B_0 field inhomogeneities, scanner drift, gradient coil stability, signal to noise ratio, and software upgrades (Veenith et al., 2013). Thus, it seems even more likely to observe imaging findings that are incongruent with other research labs using different scanners, especially when they utilize altered imaging acquisition specifications.

Lastly, there may be better methods to assess social functioning and social cognition than were employed in this study. For the SLOF, we used only the self-report form, though there are also interviewer and informant versions. Research shows that individuals with schizophrenia tend to overestimate their functional abilities and that self-report assessments often do not converge with objective data or informant report of real-world functioning (McKibbin, Patterson, & Jeste, 2004; Sabbag et al., 2011). Further, the interview-based version of the SLOF, but not the self-report or informant versions, is related to functional capacity (Sabbag et al., 2011). Karlsgodt and colleagues (2009) found that FA in the ILF contributed social and occupational functioning, and they examined functioning through an interview-based assessment. Therefore, our study may have been improved by also administering the interviewer version of the SLOF. Regarding social cognition, studies which have found a relation between white matter microstructure and social cognition administered different social cognitive measures than those used in this study. Although all assessments targeted emotion processing and theory of mind as ours did, there may be subtle differences captured by the other tasks that are more impacted by white matter abnormalities. Our study may have been improved by administering several emotion processing and theory of mind tasks and then aggregating them into composite observed or latent variables. This approach may be particularly appropriate for RDoC studies to reduce problems posed by measurement error (Lilienfeld, 2014).

Limitations

The current study had several limitations. Though we had intended to recruit a robust sample, due to recruitment and data collection challenges with individuals with a serious mental illness, our sample size was small. Given the present sample size, we were limited in statistical power and the potential to detect significant associations between white matter microstructure, social cognition, and functioning. Further, our sample was limited in regard to representation of mood disorders with psychotic features, which may have negatively impacted our aim of sampling the full dimensional continuum from healthy to pathological. Recently published RDoC studies of psychotic samples have recruited a roughly equal number of participants with schizophrenia, other psychotic disorders, and normal controls (Sabharwal et al., 2016; Sabharwal et al., 2017). Additionally, all of the clinical participants were taking medication, and many of them were prescribed several psychotropic medications. This may not have significantly impacted our results though as most cross-sectional and longitudinal studies have failed to find a relation between white matter integrity and dosage of antipsychotic drugs or cumulative drug exposure in individuals with schizophrenia spectrum disorders and bipolar disorder (for a review, see Kyriakopoulos et al., 2011). A final sample limitation is that we recruited a largely racially homogenous sample (i.e., 85% Black), which decreases the generalizability of our findings.

Another study limitation is our decision to restrict the clinical sample to those with a history of clinically significant psychotic symptoms rather than extend recruitment to other clinical samples with social disability (e.g., social anxiety disorder, non-psychotic mood disorders). We decided to focus on those with a documented history of treatment for clinically significant psychotic symptoms because social disability is a particularly severe and chronic problem in this population, and psychotic disorders share environment risk factors, endophenotypes, and neural substrates (Pishva et al., 2014).

A final potential issue is that our study employed a standard high-angular resolution diffusion-weighted image (HARDI) protocol. Standard DTI measures may not be the optimal method to examine the crossing fiber tracts (e.g., UF and ILF). A potential hindrance to this methodology is that within a single voxel only one primary direction of diffusion can be calculated, despite the fact that there are many axons within a voxel (Tuch, Reese, Wiegel, & Wedeen, 2003). Because only the mean of the primary direction is calculated, this may result in a pattern of globally reduced FA in a particular region of interest, even if FA is high in the different crossing fibers. Other types of methodologies, such as q-ball imaging, measure diffusion without making assumptions about the underlying white matter microstructure and can resolve multiple intravoxel fiber orientations (Tuch, 2004). Advanced DTI techniques to quantify the complexity of fiber crossing are currently in development (Riffert, Schreiber, Anwander, & Knosche, 2014). For example, multi b-value diffusion imaging has been developed based on q-space protocols for in-vivo mapping of water diffusion in the brain (Clark, Hedehus, & Moseley, 2002; Wu et al., 2011), and research shows that this is a more sensitive measure among non-crossing fiber tracts (e.g., corpus callosum) than standard DTI-FA (Kochunov, Chiappelli, & Hong, 2013). However, the methods for this protocol have not yet been extended to crossing fiber tracts, and thus researchers should consider employing this methodology in the future after the statistical analysis methods have been developed.

Conclusions

This study extended previous work by examining the contribution of white matter integrity to social cognition and social functioning in a transdiagnostic sample of individuals with psychosis spectrum disorders and healthy controls through an RDoC approach. Further, we assessed the associations between social cognition, social functioning, general cognitive ability, and negative symptoms. As seen in previous work, negative symptoms and social cognition were modestly related to general cognitive ability, though represented distinct domains. Additionally, negative symptoms contributed to social functioning, with experiential negative symptoms showing a more robust relationship with functioning than expressive negative symptoms. Differential relations were found with regard to our social cognition measures: only theory of mind and not emotion processing contributed to greater expressive negative symptoms and functional impairment. Finally, this study did not produce the expected relations between white matter microstructure and social cognition and functioning. We encourage future researchers to recruit larger sample sizes when conforming to the RDoC approach, administer several measures of social cognition and social functioning to create latent variables, and consider novel imaging methods (e.g., q-ball) which better address the challenges associated with crossing fiber tracts.

Appendix A: Clinical Assessment Interview for Negative Symptoms (CAINS)

Overall Introduction: *In this interview, I'll be asking you some questions about things you have been doing over the past week. In the first section, I am going to ask you some questions about your family, romantic partners, and friends, including how motivated you have been to spend time with them and how you felt when you were around them.*

I. SOCIAL (MOTIVATION & ENJOYMENT)

Ratings are based on two domains: A) Family relationships B) Friendships The item ratings are based on reports of the person's experiences, including the degree to which the person values and desires close social bonds and is motivated to seek out and sustain interactions with other people, and observable behaviors, namely, the extent to which the person initiates, actively engages in, and persists in interactions with others.

Item 1 Rating -- Family

0 = No impairment: VERY INTERESTED in and highly values close family bonds as one of the most important parts of life. Strongly desires and is highly motivated to be in contact with family. Regularly initiates and persists in interactions with family and actively engages in these interactions; good and bad times are openly discussed. Well within normal limits.

1 = Mild deficit: GENERALLY INTERESTED in and values close family bonds though response suggests some minor or questionable reduction. Generally desires and is motivated to maintain contact with family. Has a close relationship with family member(s) in which good and bad times can be discussed. Mild deficit in initiating and persisting in regular interactions with family – generally actively engaged when interactions occur.

2 = Moderate deficit: SOMEWHAT INTERESTED in family relationships and considers them somewhat important. May occasionally miss close connections with family but is only somewhat motivated to seek out interaction with family. Notable deficit in initiating and persistently engaging in interactions; discussion of good and bad times is limited. Interactions with family members may occur but are largely superficial and participation is best characterized as "going through the motions"; interactions are more likely initiated by family with mostly passive involvement of the person.

3 = Moderately severe deficit: LITTLE INTEREST in family relationships (could "take it or leave it") and does not describe family bonds as important. Describes hardly any motivation and minimal effort to have close family relationships. Rarely has discussion of good and bad times with family members. Contact and engagement with family is superficial and passive with almost all initiation and efforts to engage coming from others.

4 = Severe deficit: NO INTEREST in family relationships and does not consider them at all important. Prefers to be alone and is not at all motivated to be with family. If person does see family, it is done so grudgingly, passively and with no interest. **9 = Not rated:** All relatives are deceased or dangerous, or person is raised in highly unstable conditions outside of a family context (e.g., frequently shifting to different foster homes or facilities) (Note: this rating should be used only in rare circumstances)

ITEM 2 Rating– Friendships

0 = No impairment: VERY INTERESTED in and highly values friendships as one of the most important parts of life. Strongly desires and is very motivated to engage in friendships. Regularly initiates and persists in interactions with friends and actively engages in these interactions; good and bad times are openly discussed. Well within normal limits.

1 = Mild deficit: GENERALLY INTERESTED in and values friendships though response suggests some minor or questionable reduction. Generally desires and is motivated to engage in friendships. Has friendships in which good and bad times can be discussed though this may be less consistent. Mild deficit in initiating or persistently engaging during interactions with friends. If no friends, misses friendships, is motivated to have friends, and makes efforts to seek out friends.

2 = Moderate deficit: SOMEWHAT INTERESTED in friendships and considers them somewhat important. May occasionally miss close connections with friends and is somewhat motivated to have friends. Notable deficit in initiating and persistently engaging in interactions; discussion of good and bad times is limited. Interactions with friends may occur but are largely superficial and participation is best characterized as "going through the motions"; interactions are initiated by others with mostly passive involvement of the person. If no friends, is only somewhat motivated to have friends and rarely if ever seeks our friends.

3 = Moderately severe deficit: LITTLE INTEREST in friendships (could "take it or leave it") and does not describe friends as important. Describes hardly any motivation to have friendships, and would just as soon be alone. Contact and engagement with friends is superficial and passive with almost all initiation and efforts to engage coming from others.

4 = Severe deficit: NO INTEREST in friendships and does not consider them at all important. Prefers to be alone and is not at all motivated to have friends.

Item 3 Rating – Frequency of pleasurable social activities

0 = No impairment: Pleasure experienced daily.
1 = Mild deficit: Pleasure experienced 5 - 6 days.
2 = Moderate deficit: Pleasure experienced 3 - 4 days.
3= Moderately severe deficit: Pleasure experienced 1 - 2 days.

4 = Severe deficit: No pleasure reported.

ITEM 4 Rating – Frequency of expected pleasurable social activities

0 = No impairment: Expecting 7 or more pleasurable experiences.
1 = Mild deficit: Expecting enjoyment from 5-6 pleasurable experiences. **2**
= Moderate deficit: Expecting enjoyment from 3-4 pleasurable experiences.
3 = Moderately severe deficit: Expecting 1-2 pleasurable experiences.
4 = Severe deficit: Expecting NO pleasurable experiences.

II. VOCATIONAL (MOTIVATION AND ENJOYMENT)

The item ratings are based on reports of internal experiences, including the degree to which the person values and desires vocational activities and is motivated to seek out and sustain these activities, and observable behaviors, namely, the extent to which the person initiates, actively engages in, and persists in vocational activities. Roles considered in this category include paid employment, volunteer work, caregiver for another person (not own children), or vocational rehabilitation-related activities.

Introduction: *Now I am going to ask you some questions about work and school, including how motivated you have been for work or school activities and how you felt while doing these things over the past week. The item ratings are based on reports of internal experiences, including the degree to which the person values and desires productive work or school activities and is motivated to seek out and sustain these activities, and observable behaviors, namely, the extent to which the person initiates, actively engages in, and persists in work or school activities.*

ITEM 5 Rating – Motivation for Work/vocational/school activities

0 = No impairment: Person is VERY MOTIVATED to seek out work or school, or new opportunities in work or school; initiates and persists in work, school, or job-seeking on a regular basis, well within normal limits.

1 = Mild deficit: Person is GENERALLY MOTIVATED to seek out work or school or new opportunities in work or school; a mild deficit in initiating and persisting; may report instances of initiating, but with moderate persistence.

2= Moderate deficit: Person is SOMEWHAT MOTIVATED to seek out work or school or new opportunities in work or school; notable deficit in initiating; may have initiated activities, but needed reminders on multiple occasions, and/or not initiated any new activities, and/or not persisted for very long.

3 = Moderately severe deficit: Person is only SLIGHTLY MOTIVATED to seek out work or school or new opportunities in work or school; significant deficit in initiating;

may have needed constant reminders, and/or initiated a few activities; did not persist for very long.

4 = Severe deficit: Person is NOT AT ALL MOTIVATED to seek out work / school; nearly total lack of initiation and persistence in work, school, or job seeking.

9 = Not rated: Person has been in the hospital, or has been on vacation/break from vocational role during the prior week.

ITEM 6 Rating – Frequency of expected pleasurable vocational activities

0 = No impairment: Expecting 7 or more pleasurable experiences.
1 = Mild deficit: Expecting enjoyment from 5-6 pleasurable experiences. **2 = Moderate deficit**: Expecting enjoyment from 3-4 pleasurable experiences.
3 = Moderately severe deficit: Expecting 1-2 pleasurable experiences.
4 = Severe deficit: Expecting NO pleasurable experiences.
9 = Not rated: Will be on vacation/break from regular vocational role the following week.

III.RECREATION (MOTIVATION & ENJOYMENT)

The item ratings are based on reports of internal experiences, including the degree to which the person values and desires recreational activities and is motivated to seek out and sustain these activities, and observable behaviors, namely, the extent to which the person initiates, actively engages in, and persists in recreational activities.

Introduction: *In the next section, I am going to ask you some questions about what you do in your free time – any hobbies or recreational activities. I will ask about your motivation and feelings about the things that you have done in your free time over the past week.*

ITEM 7 Rating – Hobbies/recreation/pastimes

0 = No impairment: Person is VERY MOTIVATED to seek out hobbies and recreational activities; initiates and persists in hobbies and recreational activities on a regular basis, well within normal limits.

1 = Mild deficit: Person is GENERALLY MOTIVATED to seek out hobbies and recreational activities; a mild deficit in initiating and persisting; may report initiating hobbies, but with moderate persistence.

2= Moderate deficit: Person is SOMEWHAT MOTIVATED to seek out hobbies and recreational activities; notable deficit in initiating; may have initiated some activities and/or not persisted for very long. Others were somewhat more likely to initiate hobbies or activities.

3 = Moderately severe deficit: Person is only SLIGHTLY MOTIVATED to seek out hobbies and recreational activities; significant deficit in initiating and persisting; may have initiated a few activities and not persisted for very long. Others were much more likely to initiate hobbies or prompt initiation.

4 = Severe deficit: Person is NOT AT ALL MOTIVATED to seek out hobbies and recreational activities; nearly total lack of initiation and persistence in hobbies or recreational activities

ITEM 8 Rating– Frequency of pleasurable recreation past week

0 = No impairment: At least A FEW different types of pleasurable experiences, experienced daily.

1 = Mild deficit: At least A FEW different types of pleasurable experiences, experienced more days than not.

2 = Moderate deficit: 1 or 2 different types of pleasurable experiences, experienced more days than not.

3= Moderately severe deficit: 1 type of pleasurable experience, experienced on just a few days.

4 = Severe deficit: No pleasurable experiences.

ITEM 9 Rating – Frequency of expected pleasurable recreational activities

0 = No impairment: Expecting 7 or more pleasurable experiences.
1 = Mild deficit: Expecting enjoyment from 5-6 pleasurable experiences.
2 = Moderate deficit: Expecting enjoyment from 3-4 pleasurable experiences.
3 = Moderately severe deficit: Expecting 1-2 pleasurable experiences.
4 = Severe deficit: Expecting NO pleasurable experiences.

IV EXPRESSION

Note: all ratings are based on observations of behavior throughout the interview and responses to the specific emotional probe questions in this section. Be sure to ask questions that elicit BOTH positive and negative emotion. If the person does not respond to the prompts asking about emotional experiences, items can be rated based on the responses to other questions during the interview. At the end of the subscale, note the basis for the ratings.

ITEM 10 Rating – Facial Expression

0 = No impairment: WITHIN NORMAL LIMITS; frequent expressions throughout the interview.

1 = Mild deficit: MILD DECREASE in the frequency of facial expressions, with limited facial expressions during a few parts of the interview.

2= Moderate deficit: NOTABLE DECREASE in the frequency of facial expressions, with diminished facial expressions during several parts of the interview.

3 = Moderately severe deficit: SIGNIFICANT LACK of facial expressions, with only a few changes in facial expression throughout most of the interview.

4 = Severe deficit: NEARLY TOTAL LACK of facial expressions throughout the interview.

Item 11 Rating – Vocal Expression

0 = No impairment: WITHIN NORMAL LIMITS. Normal variation in vocal intonation across interview. Speech is expressive and animated.

1 = Mild deficit: MILD DECREASE in vocal intonation. Variation in intonation occurs with a limited intonation during a few parts of the interview.

2 = Moderate deficit: NOTABLE DECREASE in vocal intonation. Diminished intonation during several parts of the interview. Much of speech is lacking variability in intonation but prosodic changes occur in several parts of the interview.

3 = Moderately severe deficit: SIGNIFICANT LACK of vocal intonation with only a few changes in intonation throughout most of the interview. Most of speech is flat and lacking variability, only isolated instance of prosodic change

4 = Severe deficit: NEARLY TOTAL LACK OF change in vocal intonation with characteristic flat or monotone speech throughout the interview.

ITEM 12 Rating – Expressive Gestures

0 = No impairment: WITHIN NORMAL LIMITS; uses frequent gestures of the interview.

1 = Mild deficit: MILD DECREASE in the frequency of expressive gestures, with limited gestures in a few parts of the interview.

2= Moderate deficit: NOTABLE DECREASE in the frequency expressive gestures, with lack of gestures during several parts of the interview.

3 = Moderately severe deficit: SIGNIFICANT LACK of expressive gestures, with only a few gestures throughout most of the interview.

4 = Severe deficit: NEARLY TOTAL LACK of expressive gestures.

ITEM 13 Rating – Quantity of Speech

0 = No impairment: NORMAL AMOUNT of speech throughout the interview. Replies provide sufficient information with frequent spontaneous elaboration.

1 = Mild deficit: MILD DECREASE in the quantity of speech, with brief responses during a few parts of the interview.

2 = Moderate deficit: NOTABLE DECREASE in speech output, with brief responses during several parts of the interview.

3 = Moderately severe deficit: SIGNIFICANT LACK of speech, with very brief answers (only several words) in responses throughout most of the interview.

4 = Severe deficit: All or nearly all replies are one or two words throughout the entire interview

Appendix B: Brief Psychiatric Rating Scale (BRPS)

SCALE ITEMS AND ANCHOR POINTS

Rate items 1-14 on the basis of patient's self-report. Note items 7, 12, and 13 are also rated on the basis of observed behavior. Items 15-24 are rated on the basis of observed behavior and speech.

1. Somatic Concern
2. Anxiety
3. Depression
4. Suicidality
5. Guilt
6. Hostility
7. Elevated Mood
8. Grandiosity
9. Suspiciousness
10. Hallucinations
11. Unusual Thought Content
12. Bizarre Behavior
13. Self-Neglect
14. Disorientation
15. Conceptual Disorganization
16. Blunted Affect
17. Emotional Withdrawal
18. Motor Retardation
19. Tension
20. Uncooperativeness
21. Excitement
22. Distractibility
23. Motor Hyperactivity
24. Mannerisms and Posture

Appendix C: Specific Levels of Functioning (SLOF)

Instructions: Circle the number that best describes your *typical* level of functioning on each item below. Mark only one number for each item. Be sure to mark all items.

Typical is defined as follows:
Highly typical = Very much describes your behavior or level of functioning
Generally typical = Usually describes your behavior or level of functioning
Somewhat typical= Occasionally describes your behavior or level of functioning
Generally untypical= Rarely describes your behavior or level of functioning
Highly untypical= Does not describe your behavior or level of functioning at all

Social Functioning

A. Interpersonal Relationships

Item	Rating				
	Highly Typical	Generally Typical	Somewhat Typical	Generally Untypical	Highly Untypical
1. Accept contact with others	5	4	3	2	1
2. Initiate contact with others	5	4	3	2	1
3. Communicate effectively	5	4	3	2	1
4. Engage in activities without prompting	5	4	3	2	1
5. Participate in groups	5	4	3	2	1
6. Form and maintains friendships	5	4	3	2	1
7. Ask for help when needed	5	4	3	2	1

B. Social Acceptability

Item	Rating				
	Never	Rarely	Sometimes	Frequently	Always
8. Regularly argue with others	5	4	3	2	1
9. Has physical fights with others	5	4	3	2	1
10. Destroys property	5	4	3	2	1
11. Physically abuses self	5	4	3	2	1
12. Is fearful, crying, clinging	5	4	3	2	1
13. Takes property from others without permission	5	4	3	2	1

Community Living Skills

C. Activities

Item	Rating					
	Totally Self Sufficient	Needs Verbal Advice or Guidance	Needs Some Physical Help or Assistance	Needs Substantial Help	Totally Dependent	No Opportunity to perform
14. Household responsibilities (house cleaning, cooking, washing clothes)	5	4	3	2	1	7
15. Shopping (selection of items, choice of stores, payment at register)	5	4	3	2	1	7
16. Handling personal finances (budgeting, paying bills)	5	4	3	2	1	7

Item	Rating					
	Totally Self Sufficient	Needs Verbal Advice or Guidance	Needs Some Physical Help or Assistance	Needs Substantial Help	Totally Dependent	No Opportunity to perform
17. Use of telephone (getting number, dialing, speaking, listening)	5	4	3	2	1	7
18. Traveling from residence without getting lost	5	4	3	2	1	7
19. Use of public transportation (selecting route, using timetable, paying fares, making transfers)	5	4	3	2	1	7
20. Use of leisure time (reading , visiting friends, listening to music)	5	4	3	2	1	7
21. Recognizing and avoiding common dangers (traffic safety, fire safety)	5	4	3	2	1	7
22. Self-medication (understanding purpose, taking as prescribed, recognizing side effects)	5	4	3	2	1	7
23. Use of medical and other community services (knowing whom to contact, how, and when to use)	5	4	3	2	1	7
24. Basic reading, writing, and arithmetic (enough for daily needs)	5	4	3	2	1	7

D. Work Skills

Item	Rating				
	Highly Typical	Generally Typical	Somewhat Typical	Generally Untypical	Highly Untypical
25. Has employable skills	5	4	3	2	1
26. Works with minimal supervision	5	4	3	2	1
27. Is able to sustain work effort (not easily distracted, can work under stress)	5	4	3	2	1
28. Appears at appointments on time	5	4	3	2	1
29. Follows verbal instructions accurately	5	4	3	2	1
30. Completes assigned tasks	5	4	3	2	1

Appendix D: Wechsler Test of Adult Reading (WTAR)

Instructions: I will show you some words that I will ask you to pronounce. Beginning with the first word on the list, pronounce each word aloud. Start with this word (point to Item 1), and go down this column, one right after the other, without skipping any. When you finish with this column, go to the next column (point to the second column). Pronounce each work even if you are unsure. Do you understand? Ready? Begin.

1. again
2. address
3. cough
4. preview
5. although
6. most
7. excitement
8. know
9. plumb
10. decorate
11. fierce
12. knead
13. aisle
14. vengeance
15. prestigious
16. wreathe
17. gnat
18. amphitheater
19. lieu
20. grotesque
21. iridescent
22. ballet
23. equestrian
24. porpoise
25. aesthetic
26. conscientious
27. homily
28. malady
29. subtle
30. fecund
31. palatable
32. menagerie
33. obfuscate
34. liaison
35. exigency
36. xenophobia
37. ogre
38. scurrilous
39. ethereal
40. paradigm
41. perspicuity
42. plethora
43. lugubrious
44. treatise
45. dilettante
46. vertiginous
47. ubiquitous
48. hyperbole
49. insouciant
50. hegemony

Appendix E: The Hinting Task

Instructions.

I'm going to read out a set of 10 stories involving two people. Each story ends with one of the characters saying something. When I've read the stories out loud, I'm going to ask you some questions about what the character said.

Here's the first story. Listen carefully to it.

Story	**Verbatim Response 1 and score**	**Verbatim Response 2 and score**
1) long, hot journey		
2) dirty bath		
3) cookies		
4) wrinkled shirt		
5) flat broke		
6) project at work		
7) birthday present		
8) ornaments		
9) train set		
10) heavy cases		

Hinting Task: Scoring and Prompts

1) George arrives in Angela's office after a long and hot journey down the highway. Angela immediately begins to talk about some business ideas. George interrupts Angela saying:

"My, my! It was a long, hot journey down the highway!"

QUESTION: What does George really mean when he says this?

Answer: George means either “Can I have a drink” and/or “Can I have a few minutes to settle down after my journey before we start talking business.” Either of these responses would score 2.

If a correct response is not given for the first hint (e.g., the participant just replies something like “He means exactly what he says”) then introduce next part of the story / hint.

ADD: George goes on to say:
"I'm parched!"

QUESTION: What does George want Angela to do?

Answer: George wants Angela to get him or offer to get him a drink. This response would score 1. Anything else would be given a score of 0.

2) Melissa goes to the bathroom for a shower. Anne has just had a bath. Melissa notices the bath is dirty so she calls upstairs to Anne:

"Couldn't you find the Ajax, Anne?"

QUESTION: What does Melissa really mean when she says this?

Answer: Melissa means “Why didn’t you clean out the bath” or “Go and clean out the bath now.” This response would be given a score of 2 and next item would be introduced

If the participant fails to give the correct answer at this stage then:

ADD: Melissa goes on to say:
"You're very lazy sometimes, Anne!"

QUESTION: What does Melissa want Anne to do?

Answer: Melissa wants Anne to clean out the bath. This response would score 1. Any other response would be given a score of 0.

3) Gordon goes to the supermarket with his mom. They arrive at the cookie aisle. Gordon says:

"Mom! Those cookies look delicious."

QUESTION: What does Gordon really mean when he says this?

Answer: Gordon means “Please buy me some cookies, mom”

ADD: Gordon goes on to say:
"I'm hungry, mom."

QUESTION: What does Gordon want his mom to do?

Answer: Buy him some sweets.

4) Paul has to go to an interview and he's running late. While he is cleaning his shoes, he says to his wife, Jane:

"I want to wear that blue shirt but it's very wrinkled."

QUESTION: What does Paul really mean when he says this?

Answer: Paul means "Will you iron my shirt for me please?"

ADD: Paul goes on to say:
"It's in the ironing basket."

QUESTION: What does Paul want Jane to do?

Answer: Iron his shirt

5) Lucy is broke but she wants to go out in the evening. She knows that David has just been paid. She says to him:

"I'm flat broke! Things are so expensive these days."

QUESTION: What does Lucy really mean when she says this?

Answer: Lucy means “Will you lend me some money David ?” OR “Will you take me out tonight and pay?”

ADD: Lucy goes on to say:

"Oh well, I suppose I'll have to miss my night out."

QUESTION: What does Lucy want David to do?

Answer: She wants David to lend her money or offer to take her out and pay.

6) Donald wants to run a project at work but Richard, his boss, has asked someone else to run it. Donald says:

"What a pity. I'm not too busy at the moment."

QUESTION: What does Donald really mean when he says this?

Answer: Donald means “ Please change your mind Richard and give the project to me”

ADD: Donald goes on to say:
"That project is right up my street."

QUESTION: What does Donald want Richard to do?

Answer: Change his mind and give the project to him to run.

7) Rebecca's birthday is approaching. She says to her Dad:

"I love animals, especially dogs."

QUESTION: What does Rebecca really mean when she says this?

Answer: “Will you buy me a dog for my birthday Dad?”

ADD: Rebecca goes on to say:
"Will the pet shop be open on my birthday, Dad?"

QUESTION: What does Rebecca want her dad to do?

Answer: to say he’ll buy her a dog for her birthday/ buy her a dog for her birthday

8) Betty and Michael moved into their new house a week ago. Betty has been unpacking some ornaments. She says to Michael:

"Have you unpacked those shelves we bought, Michael?"

QUESTION: What does Betty really mean when she says this?

Answer: Betty means “Will you put those shelves up now please?”

ADD: Betty goes on to say:

"If you want something doing you have to do it yourself!"

QUESTION: What does Betty want Michael to do?

Answer: Put the shelves up.

9) Jessica and Max are playing with a train set. Jessica has the blue train and Max has the red one. Jessica says to Max:

"I don't like this train."

QUESTION: What does Jessica really mean when she says this?

Answer: Jessica means “I want your train and you can have mine.”

ADD: Jessica goes on to say:
"Red is my favorite color."

QUESTION: What does Jessica want Max to do?

Answer: swap trains

10) Patsy is just getting off the train with three heavy cases. John is standing behind her. Patsy says to John:

"Gosh! These cases are a nuisance."

QUESTION: What did Patsy really mean when she said this?

Answer: Patsy means “ Would you help me with my luggage please”

ADD: Patsy goes on to say:
"I don't know if I can manage all three."

QUESTION: What does Patsy want John to do?

Answer: help her with her case

Appendix F: Bell Lysaker Emotion Recognition Task (BLERT)

Instructions: Now you are going to watch a video with 21 different scenes. After you see and hear the person talking, tell me which of the words on the response card describes the emotion of the person speaking.
Note: If the participant does not provide a ready answer (~ 5 seconds), you may say, "What is your best guess?"

Happiness	**Sadness**	**Surprise**	**Disgust**	**Anger**	**Fear**	**No Emotion**
A	B	C	D	E	F	G

…………………………………………………………………………………………

1. A B C D E F
2. A B C D E F
3. A B C D E F
4. A B C D E F
5. A B C D E F
6. A B C D E F
7. A B C D E F
8. A B C D E F
9. A B C D E F
10. A B C D E F
11. A B C D E F
12. A B C D E F
13. A B C D E F
14. A B C D E F
15. A B C D E F
16. A B C D E F
17. A B C D E F
18. A B C D E F
19. A B C D E F
20. A B C D E F
21. A B C D E F

References

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature, 372*(6507), 669-672.

Allen, D. N., & Barchard, K. A. (2009). Identification of social cognition construct for the WAIS-III. *Applied Neuropsychology, 16*(4), 262-274.

Allen, D. N., Frantom, L. V., Strauss, G. P., & van Krammen, D. P. (2005). Differential patterns of premorbid academic and social deterioration in patients with schizophrenia. *Schizophrenia Research, 75*(2-3), 389-397.

Amaral, D. G., & Price, J. L. (1984). Amygdalo-cortical projections in the monkey (Macaca fascicularis). *Journal of Comparative Neurology, 230*(4), 465-496.

Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: The medial frontal cortex and social cognition. *Nature Reviews Neuroscience, 7*(4), 268-277.

Andersen, J., Larsen, J. K., Schultz, V., Nielsen, B. M., Korner, A., Behnke, K., Munk-Andersen, E., Butler, B., Allerup, P., & Bech, P. (1989). The Brief Psychiatric Rating Scale. Dimension of schizophrenia – the reliability and construct validity. *Psychopathology, 22*(2-3), 168-176.

Bahnemann, M., Dziobek, I., Prehn, K., Wolf, I., & Heekeren, H. R. (2010). Sociotopy in the temporoparietal cortex: Common versus distinct processes. *Social Cognitive and Affective Neuroscience, 5*(1), 48-58.

Baslow, M. H. (2002). Evidence supporting a role for N-acetyl-L-aspartate as a molecular water pump in myelinated neurons in the central nervous system. An analytical review. *Neurochemistry International, 40*(4), 295-300.

Bell, M. D., Corbera, S., Johannesen, J. K., Fiszdon, J. M., & Wexler, B. E. (2011). Social cognitive impairments and negative symptoms in schizophrenia: Are there subtypes with distinct functional correlates? *Schizophrenia Bulletin, 39*(1), 186 - 196.

Bellack, A. S., Morrison, R. L., Wixted, J. T., & Mueser, K. T. (1990). An analysis of social competence in schizophrenia. *The British Journal of Psychiatry, 156*(6), 809-818.

Bertrand, M. C., Sutton, H., Achim, A. M., Malla, A. K., & Lepage, M. (2007). Social cognitive impairments in first episode psychosis. *Schizophrenia Research, 95*(1-3), 124-133.

Blanchard, J. J., Bradshaw, K.R., Garcia, C P., Nasrallah, H. A., Harvey, P. D., Casey, D., Csoboth, C. T., Hudson, J. I., Julian, L., Lentz, E., Nuechterlein, K. H., Perkins, D. O., Skale, T. G., Snowden, L. R., Tandon, R., Tek, C., Velligan, D., Vinogradov, S., & O'Gorman, C. (2017). Examining the reliability and validity of the Clinical Assessment Interview for Negative Symptoms within the Management of Schizophrenia in Clinical Practice (MOSAIC) multisite national study. *Schizophrenia Research, 185*, 137-143

Blanchard, J. J., Park, S. G., Catalano, L. T., & Bennett, M. E. (2015). Social affiliation and negative symptoms in schizophrenia: Examining the role of behavioral skills and subjective responding. Schizophrenia *Research, 168*(1-2), 491-497.

Boekel, W., Wagenmakers, E., Belay, L., Verhagen, J., Brown, S., Forstmann, B. U. (2015). A purely confirmatory replication study of structural brain-behavior correlations. *Cortex, 66*, 115-133.

Brekke, J. S., Kay, D. D., Kee, K. S., & Green, M. F. (2005). Biosocial pathways to f functional outcome in schizophrenia. *Schizophrenia Research, 80*(2-3), 213-225.

Browne, J., Penn, D. L., Raykov, T., Pinkham, A. E., Kelsven, S., Buck, B., & Harvey, P. D. (2016). Social cognition in schizophrenia: Factor structure of emotion processing and theory of mind. *Psychiatry Research, 242*, 150-156.

Brune, M., Lissek, S., Fuchs, N., Witthaus, H., Nicolas, V., Juckel, G., & Tegenthoff, M. (2008). An fMRI study of theory of mind in schizophrenic patients with 'passivity' symptoms. *Neuropsychologia, 46*(7), 1992-2001.

Brunet-Gouet, E., & Decety, J. (2006). Social brain dysfunctions in schizophrenia: A review of neuroimaging studies. *Psychiatry Research: Neuroimaging, 148*(2-3), 75-92.

Bryson, G., Bell, M., & Lysaker, P. (1997). Affect recognition in schizophrenia: A function of global impairment or a specific cognitive deficit. *Psychiatry Research, 71*(2), 105-113.

Buck, B.E., Pinkham, A. E., Harvey, P. D., & Penn, D. L. (2016). Revisiting the validity of measures of social cognitive bias in schizophrenia: Additional results from the Social Cognition Psychometric Evaluation (SCOPE) study. *British Journal of Clinical Psychology, 55*(4), 441-454.

Button, K. S., Ioannidis, J. P., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S., & Munago, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience, 14*, 365-376

Butzlaff, R. L., & Hooley, J. M. (1998). Expressed emotion and psychiatric relapse: A meta-analysis. *Archives of General Psychiatry, 55*(6), 547-552.

Calder, A. J., Keane, J., Manly, T., Sprengelmeyer, R., Scott, S., Nimmo-Smith, I., & Young, A.W. (2003). Facial expression recognition across the adult life span. *Neuropsychologia,41*(2), 195-202.

Cannon, T. D., Cadenhead, K., Cornblatt, B., Woods, S. W., Addington, J., Walker, E., Seidman, L. J., Perkins, D., Tsuang, M., McGlashan, T., & Heinssen, R. (2008). Prediction of psychosis in youth at clinical high risk: A multisite longitudinal study in North America. *Archives of General Psychiatry, 65*(1), 28-39.

Carrington, S. J., & Bailey, A. J. (2009). Are there theory of mind regions in the brain? A review of the neuroimaging literature. *Human Brain Mapping, 30*(8), 2313-2335.

Carter, C. S., Barch, D. M., Gur, R., G., R., Pinkham, A., & Ochsner, K. (2009). CNTRICS final task selection: Social cognitive and affective neuroscience-based measures. *Schizophrenia Bulletin, 35*(1), 153-162.

Catani, M., Jones, D. K., & Donato, R. (2003). Occipito-temporal connections in the human brain. *Brain, 126*(9), 2093-2107.

Chung, Y. S., Kang, D. S., Shin, N. Y., Yoo, S. Y., & Kwon, J. S. (2008). Deficit theory of mind in individuals at ultra-high-risk for schizophrenia. *Schizophrenia Research, 99*(1-3), 111-118.

Clark, C. A., Hedehus, M., & Moseley, M. E. (2002). In vivo mapping of the fast and slow diffusion tensors in human brain. *Magnetic Resonance in Medicine, 47*(4), 623-628.

Cotter, J., Bartholomeusz, C., Papas, A., Allott, K., Nelson, B., Yung, A. R., & Thompson, A. (2017). Examining the association between social cognition and functioning in individuals at ultra-high risk for psychosis. *Australian and New*

Zealand Journal of Psychiatry, 51(1), 83-92.

Conrad, A. J., Abebe, T., Austin, R., Forsythe, S., & Scheibel, A. B. (1991). Hippocampal pyramidal cell disarray in schizophrenia as a bilateral phenomenon, *Archives of General Psychiatry, 48*(5), 413-417.

Corcoran, R., Mercer, G., & Frith, C. D. (1995). Schizophrenia, symptomatology and social influence: Investigating 'theory of mind' in people with schizophrenia. *Schizophrenia Research, 17*(1), 5-13.

Couture, S. M., Granholm, E. L., & Fish, S. C. (2011). A path model investigation of neurocognition, theory of mind, social competence, negative symptoms, and real-world functioning in schizophrenia. *Schizophrenia Research, 125*(2-3), 152-160.

Couture, S. M., Penn, D. L., & Roberts, D. L. (2006). The functional significance of social cognition in schizophrenia: A review. *Schizophrenia Bulletin, 32*(S1), 44-63.

Das, P., Lagopoulos, J., Coulston, C. M., Henderson, A. F., & Malhi, G. S. (2012). Mentalizing impairment in schizophrenia: A functional MRI study. *Schizophrenia Research, 134*(2-3), 158-164.

Devries, A. C., Glasper, E. R., & Detillion, C. E. (2003). Social modulation of stress response. *Physiology & Behavior, 79*(3), 399-407.

Dong, D., Wang, Y., Chang, X., Jiang, C., Klugah-Brown, B., Luo, C., & Yao, D. (2017). Shared abnormality of white matter integrity in schizophrenia and bipolar disorder: A comparative voxel-based meta-analysis. *Schizophrenia Research, 185*, 41-50.

Dyck, D. G., Short, R., & Vitaliano, P. P. (1999). Predictors of burden and infectious illness in schizophrenia caregivers. *Psychosomatic Medicine, 61*(4), 411-419.

Edwards, J., Pattison, P. E., Jackson, H. J., & Wales, R. J. (2001). Facial affect and affective prosody recognition in first-episode schizophrenia. *Schizophrenia Research, 48*(2-3), 235-253.

Feinberg, I. (1982). Schizophrenia: Caused by a faulty in programmed synaptic elimination during adolescence? *Journal of Psychiatric Research, 17*(4), 319-334.

First, M. B., Williams, J. B. W., Karg, R. S., & Spitzer, R. L. (2015). Structured Clinical Interview for DSM-5 – Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV). Arlington, VA, American Psychiatric Association.

Fiszdon, J. M., & Reddy, L. F. (2012). Review of social cognitive treatments for psychosis. *Clinical Psychology Review, 32*(8), 724-740.

Fornito, A., Yucel, M., Patti, J., Wood, S. J., & Pnatelis, C. (2009). Mapping grey matter reductions in schizophrenia: An anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophrenia Research, 108*(1-3), 104-113.

Fusar-Poli, P., Deste, G., Smieskova, R., Barlati, S., Yung, A. R., Howes, O., Stieglitz, R-D., Vita, A., McGuire, P., & Borgwardt, S. (2012). Cognitive functioning in prodromal psychosis: A meta-analysis. *JAMA Psychiatry, 69*(6), 562-571.

Ge, Y., Grossman, R. I., Babb, J. S., Rabin, M. L., Mannon, L. J., & Kolson, D. L. (2002). Age related total grey matter and white matter changes in normal adult brain part II: Quantitative magnetization transfer ratio histogram analysis. *American Journal of Neuroradiology, 23*(8), 1334-1341.

Ghashghaei, H. T., Hilgetag, C. C., & Barbas, H. (2007). Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *Neuroimage, 34*(3), 905-923.

Ghashghaei, H. T., & Barbas, H. (2002). Pathways for emotion: interactions of prefrontal and anterior temporal amygdala of the rhesus monkey. *Neuroscience, 115*(4), 1261-1279.

Giuliano, A. J., Li, H., Mesholam-Gately, R. I., Sorenson, S. M., Woodberry, K. A., & Seidman, L. J. (2012). Neurocognition in the psychosis risk syndrome: A quantitative and qualitative review. *Current Pharmaceutical Design, 18*(4), 399-415.

Gogtay, N., Lu, A., Leow, A. D., Klunder, A. D., Lee, Agatha, D., Chavez, A., Greenstien, D.,Giedd, J. N., Toga, A. W., Rapoport, J. L., & Thompson, P. M. (2008). Three dimensional brain growth abnormalities in childhood-onset schizophrenia visualized by using tensor-based morphometry. *PNAS Proceedings of the National Academy of Sciences of the United States of America, 105*(41), 15979-15984.

Gray, J. A., & Roth, B. L. (2007). Molecular targets for treating cognitive dysfunction in schizophrenia. *Schizophrenia Bulletin, 33*(5), 1100-1119.

Gross, T. F. (2009). Own-ethnicity bias in the recognition of black, East Asian, Hispanic, and white faces. *Basic and Applied Social Psychology, 31*(2), 128-135.

Green, M. F., & Horan, W. P. (2010). Social cognition in schizophrenia. *Current Directions in Psychological Science, 19*(4), 243-248.

Green, M. F., Penn, D. L., Bentall, R., Carpenter, W. T., Gaebel, W., Gur, R. C., Kring, A. M., Park, S., Silverstein, S. M., & Heinssen, R. (2008). Social cognition in schizophrenia: An NIMH workshop on definitions, assessment, and research opportunities. *Schizophrenia Bulletin, 34*(6), 1211-1220.

Gur, R. E., McGrath, C., Chan, R. M., Schroeder, L., Turner, T., Turetsky, B. I., Kohler, C., Alsop, D., Maldjian, J., Ragland, J. D., & Gur, R. C. (2002). An fMRI study of facial emotion processing in patients with schizophrenia. *The American Journal of Psychiatry, 159*(12), 1992-1999.

Habel, U., Klein, M., Shah, N. J., Toni, I., Ziles, K., Falkai, P., & Schneider, F. (2004). Genetic load on amygdala hypofunction during sadness in non-affected brothers of schizophrenia patients. *The American Journal of Psychiatry, 161*(10), 1806-1813.

Häfner, H., Nowotny, B., Löffler, W., an der Heiden, W., & Maurer, K. (1995). When and how does schizophrenia produce social deficits? *European Archives of Psychiatry and Clinical Neuroscience*, *246*(1), 17-28.

Harvey, P. D., Docherty, N. M., Serper, M. R., & Rasmussen, M. (1990). Cognitive deficits and thought disorder: II. An 8-month followup study. *Schizophrenia Bulletin, 16*(1), 147-156.

Harvey, P. D., Heaton, R. K., Carpenter, W. T., Green, M. F., Gold, J. W., & Schoenbaum, M. (2012). Functional impairment in people with schizophrenia: Focus on employability and eligibility for disability compensation. *Schizophrenia Research, 140*(1-3), 1-8.

Harvey, P. D., Koren, D., Rechenber, A., & Bowie, C. R. (2006). Negative symptoms and cognitive deficits: What is the nature of their relationship? *Schizophrenia Bulletin, 32*(2), 250-258.

Harvey, P. D., Raykov, T., Twamley, E. W., Vella, L., Heaton, R. K., & Patterson, T. L.

(2011). Validating the measurement of real-world functional outcomes: Phase I results of the VALERO study. *The American Journal of Psychiatry, 168*(11), 1195-1201.

Holt-Lunstad, J., Smith, T. B., Baker, M., Harris, T., & Stephenson, D. (2015). Loneliness and social isolation as risk factors for mortality: A meta-analytic review. *Perspectives on Psychological Science, 10*(2), 227-237.

Horan, W. P., Green, M. F., Degroot, M., Fiske, A., Hellemann, G., Kee, K., Kern, R. S., Lee, J., Sergi, M. J., Subotnik, K. L., Sugar, C. A., Ventura, J., & Nuechterlein, K. H. (2011). Social cognition in schizophrenia, part 2: 12-month stability and prediction of functional outcome in first-episode patients. *Schizophrenia Bulletin, 38*(4), 865-872.

Hornak, J., Rolls, E. T., & Wade, D. (1996). Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. *Neuropsychologia, 34*(4), 247-261.

House, J. S., Landis, K. R., & Umberson, D. (1988). Social relationships and health. *Science, 241*(4865), 540-545.

Hurford, I. M., Marder, S. R., Keefe, R. S. E., Reise, S. P., & Bilder, R. M. (2011). A brief cognitive assessment tool for schizophrenia: Construction of a tool for c clinicians. *Schizophrenia Bulletin, 37*(3), 538-545.

Inoue, Y., Yamada, K., & Kanba, S. (2006). Deficit in theory of mind is a risk for relapse of major depression. *Journal of Affective Disorders, 95*(1-3), 125-127.

Insel, T. R., Cuthbert, B. N., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *The American Journal of Psychiatry, 167*(7), 748-751.

Ioannidis, J. P. (2008). Why most discovered true associations are inflated. *Epidemiology, 19*(5), 640-648.

Iwai, E., & Yukie, M. (1987). Amygdalofugal and amygdalopetal connections with modality-specific visual cortical areas in macaques (macaca fuscata, M. mulatta, and M. fascicularis). *Journal of Comparative Neurology, 261*(3), 362-387.

Jalbrzikowski, M., Villalon-Reina, J. E., Karlsgodt, K. H., Senturk, D., Chow, C., Thompson, P. M., & Bearden, C. E. (2014). Altered white matter microstructure is associated with social cognition and psychotic symptoms in 22q11.2 microdeletion syndrome. *Frontiers in Behavioral Neuroscience, 8*:393. doi: 10.3389/fnbeh.2014.00393.

Kalin, M., Kaplan, S., Gould, F., Pinkham, A. E., Penn, D. L., & Harvey, P. D. (2015). Social cognition, social competence, negative symptoms, and social outcomes: Inter relationships in people with schizophrenia. *Journal of Psychiatric Research, 68*, 254-260.

Karlsgodt, K. H., Niendam, T. A., Bearden, C. E., & Cannon, T. D. (2009). White matter integrity and prediction of social and role functioning in subjects at ultra-high risk for psychosis. *Biological Psychiatry, 66*(6), 562-569.

Katz, S. J., Conway, C. C., Hammen, C. L., Brennan, P. A., & Najman, J. M. (2011). Childhood social withdrawal, interpersonal impairment, and young adult depression: A meditational model. *Journal of Abnormal Child Psychology, 39*(8), 1227-1238.

Keightley, M. L., Chiew, K. S., Winocur, G., & Grady, C. L. (2007). Age-related differences in brain activity underlying identification of emotion expressions in faces. *Social Cognitive and Affective Neuroscience, 2*(4), 292-302.

King, S., St-Hilaire, A., & Heidkemp, D. (2010). Prenatal factors in schizophrenia. *Current Directions on Psychological Science, 19*(4), 209-213.

Kirkpatrick, B., Fenton, W. S., Carpenter, W. T., & Marder, S. R. (2006). The NIMH-MATRICS consensus statement on negative symptoms. *Schizophrenia Bulletin, 32*(2), 214-219.

Kochunov, P., Chiappelli, J., & Hong, L.E. (2013). Permeability-diffusivity modeling vs. fractional anisotropy on white matter integrity assessment and application in schizophrenia. *NeuroImage: Clinical, 3*, 18-26.

Kochunov, P., Du, X., Moran, L.V., Sampath, H., Wijtenburg, S.A., Yang, Y., Rowland, L.M., Stein, E.A., & Hong, L.E. (2013). Acute nicotine administration effects on fractional anisotropy of cerebral white matter and associated attention performance. *Frontiers in Pharmacology, 4*:117, doi: 10.3389/fphar.2013.00117.

Kopelowicz, A., Ventura, J., Liberman, R. P., & Mintz, J. (2008). Consistency of Brief Psychiatric Rating Scale factor structure across a broad spectrum of schizophrenia patients. *Psychopathology, 41*(2), 77-84.

Krakauer, K., Ebdrup, B. H., Glenthoj, B. Y., Raghava, J. M., Nordholm, D., Randers, L., Rostrup, E., & Nordentoft, M. (2017). Patterns of white matter microstructure in individuals at ultra-high-risk for psychosis: associations to level of functioning and clinical symptoms. *Psychological Medicine, 47*(15), 2689-2707.

Kring, A. M., Gur, R. E., Blanchard, J. J., Horan, W. P., & Reise, S. P. (2013). The clinical Assessment interview for negative symptoms (CAINS): final development and validation. *American Journal of Psychiatry, 170*(2), 165-172.

Kyriakopoulos, M., Samartzis, L., Dima, D., Hayes, D., Corrigall, R., Barker, G., Correll, C., & Frangou, S. (2011). P03-111-does antipsychotic medication affect white matter in schizophrenia and bipolar? A review of diffusion tensor imaging literature. *European Psychiatry, 26*(1), 1280.

Latini, F. (2015). New insights in the limbic modulation of visual inputs: The role of the inferior longitudinal fasciculus and the Li-Am bundle. *Neurosurgical Review, 38*(1), 179-190.

Lencz, T., Smith, C. W., Auther, A., Correll, C. U., & Cornblatt, B. (2004). Nonspecific and attenuated negative symptoms in patients at clinical high-risk for schizophrenia. *Schizophrenia Research, 68*(1), 37-48.

Lewis, D. A., & Levitt, P. (2002). Schizophrenia as a disorder of neurodevelopment. *Annual Review of Neuroscience, 25*, 409-432.

Lilienfeld, S. O. (2014). The Research Domain Criteria (RDoC): An analysis of methodological and conceptual challenges. *Behaviour Research and Therapy, 62*, 129-139.

Lilienfeld, S. O., & Treadway, M. T. (2016). Clashing diagnostic approaches: DSM-ICD versus RDoC. *Annual Review of Clinical Psychology, 12*, 435-463.

Mar, R. A. (2011). The neural bases of social cognition and story comprehension. *Annual Review of Psychology, 62*, 103-134.

Marner, L., Nyengaard, J. R., Tang, Y., & Pakkenberg, B. (2003). Marked loss of myelinated nerve fibers in the human brain with age. *The Journal of Comparative*

Neurology, 462(2), 144-52.

Marwaha, S., & Johnson, S. (2004). Schizophrenia and employment: A review. *Social Psychiatry and Psychiatric Epidemiology, 39*(5), 337-349.

McKibbin, C., Patterson, T. L., & Jeste, D. V. (2004). Assessing disability in older patients with schizophrenia: Results from the WHODAS-II. *The Journal of Nervous and Mental Disease, 192*(6), 405-413.

Mehta, U. M., Thirthalli, J., Subbaksrishna, D. K., Gangadhar, B. N., Eack, S. M., & Keshavan, M. S. (2013). Social and neuro-cognition as distinct cognitive factors in schizophrenia: A systematic review. *Schizophrenia Research, 48*(1-3), 3-11.

Meier-Ruge, W., Ulrich, J., Bruhlman, M., Meier, E. (1992). Age-related white matter atrophy in the human brain. *Annals of the New York Academy of Sciences, 673,* 260-269.

Miyata, J., Yamada, M., Namiki, C., Hirao, K., Saze, T., Fujiwara, H., Shimizu, M., Kawada, R., Fukuyama, H., Sawamoto, N., Hayashi, T., & Murai, T. (2010). Reduced white matter integrity as a neural correlate of social cognition deficits in schizophrenia. *Schizophrenia Research, 119*(1-3), 232-239.

Mori, S., Wakana, S., Nagae-Petscher, L. M., & van Zijl, P. C. M. (2005). *MRI Atlas of Human White Batter.* Elsevier: Amsterdam, 284 pp.

Morris, J. S., Friston, K. J., Buchel, C., Frith, C. D., Young, A. W., Calder, A. J., & Dolan, R. J. (1998). A neuromodulary role for the human amygdala in processing emotional facial expressions. *Brain: A Journal of Neurology, 121*(1), 47-57.

Morlan, K. K., & Tan, S. (1998). Comparison of the Brief Psychiatric Rating Scale and the Brief Symptom Inventory. *Journal of Clinical Psychology*, *54*(7), 885-894.

Mugler, J. P. & Brookeman, J. R. (1990) Three-dimensional magnetization-prepared rapid gradient-echo imaging (3D MP RAGE). *Magnetic Resonance in Medicine 15*(1), 152–157.

Murray, R. M., O'Callaghan, E., Castle, D. J., & Lewis, S. W. (1992). A neurodevelopmental approach to the classification of schizophrenia. *Schizophrenia Bulletin, 18*(2), 319-332.

Nanko, S., & Moridaira, J. (1993). Reproductive rates in schizophrenia outpatients. *Acta Psychiatrica Scandinavica, 87*(6), 400-404.

Overall, J. E., & Gorham, D. R. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports, 10,* 799-812.

Pankow, A., Friedel, E., Sterzer, P., Seiferth, N., Walter, H., Heinz, A., & Schlagenhauf, F. (2013). Altered amygdala activation in schizophrenia patients during emotion processing. *Schizophrenia Research, 150*(1), 101-106.

Patrick, C. J., & Hajcak, G. (2016). RDoC: Translating promise into progress. *Psychophysioloy,53*(3), 415-424.

Penn, D. L., Keefe, R. S., Davis, S. M., Meyer, P. S., Perkin, D. O., Losardo, D., & Liberman, J. A. (2009). The effects of antipsychotic medications on emotion perception in patients with chronic schizophrenia in the CATIE trial. *Schizophrenia Research, 115*(1), 17-23.

Pinkham, A. E., Penn, D. L., Green, M. F., Buck, B., Healey, K., & Harvey, P. D. (2014). The social cognition psychometric evaluation study: Results of the expert survey and RAND panel. *Schizophrenia Bulletin, 40*(4), 813-823.

Pinkham, A. E., Penn, D. L., Green, M. F., & Harvey, P. D. (2016). Social cognition psychometric evaluation: Results of initial psychometric study. *Schizophrenia*

Bulletin,42(2), 494-504.

Pishva, E., Kenis, G., van den Hove, D., Lesch, K-P, Boks, M. P. M., van Os, J., & Rutten, B. P. F. (2014). The epigenome and postnatal environmental influences in psychotic disorders. *Social Psychiatry and Psychiatric Epidemiology, 49*(3), 337-348.

Rapoport, J. L., Giedd, J., Kumra, S., Jacobsen, L., Smith, A., Lee, P., Nelson, J., & Hamburger, S. (1997). Childhood-onset schizophrenia: Progressive ventricular change during adolescence. *Archives of General Psychiatry, 54*(10), 897-903.

Rapoport, J. L., & Gogtay, N. (2011). Childhood onset schizophrenia: Support for a progressive neurodevelopmental disorder. *International Journal of Developmental Neuroscience, 29*(3), 251-258.

Riffert, T. W., Schreiber, J., Anwander, A., & Knosche, T. R. (2014). Beyond fractional anisotropy: Extraction of bundle-specific structural metrics from crossing fiber models. *Neuroimage, 100C*, 176-191.

Roalf, D. R., Gur, R. E., Ruparel, K., Calkins, M. E., Satterthwaite, T. D., Bilker, W. B., Hakonarson, H., Harris, L. J., & Gur, R. C. (2014). Within-individual variability in neurocognitive performance: Age- and sex-related differences in children and youths from ages 8 to 21. *Neuropsychology, 28*(4), 506-518.

Rocca, P., Montemagni, C., Zappia, S., Pitera, R., Siguado M., & Bogetto F. (2014). Negative symptoms and everyday functioning in schizophrenia: A cross-sectional study in a real world setting. *Psychiatry Research, 218*(3), 284-289.

Rosenheck, R., Leslie, D., Keefe, R., McEvoy, J., Swartz, M., Perkins, D., Stroup, S., Hsiao, J. K., Lieberman, J. (2006). Barriers to employment for people with schizophrenia. *American Journal of Psychiatry, 163(*3), 411-417.

Ruocco, A. C., Reilly, J. L., Rubin, L. H., Faros, A. R., Gershon, E. S., Tamminga, C. CA., Pearlson, G. D., Hill, S. K., Keshavan, M. S., Gur, R. C., & Sweeney, J. A. (2014). Emotion recognition deficits in schizophrenia-spectrum disorders and psychotic bipolar disorder: Findings from the Bipolar-Schizophrenia Network on Intermediate phenotypes (B-SNIP) study. *Schizophrenia Research, 158*(1-3), 105-112.

Sabbag, S., Twamley, E. M., Vella, L., Heaton, R. K., Patterson, T. L., & Harvey, P. D. (2011). Assessing everyday functioning in schizophrenia: Not all informants seem equally informative. *Schizophrenia Research, 131*(1-3), 250-255.

Sabharwal, A., Kotov, R., Szekely, A., Leung, H., Barch, D. M., & Mohanty, A. (2017). Neural markers of emotional face perception across psychotic disorders and general population. *Journal of Abnormal Psychology, 126*(5), 663-678.

Sabharwal, A., Szekely, A., Kotov, R., Mukherjee, P., Leung, H., Barch, D. M., & Mohanty, A. (2016). Transdiagnostic neural markers of emotion-cognition interaction in psychotic disorders. *Journal of Abnormal Psychology, 125*(7), 907-922.

Salat, D. H., Tuch, D. S., Greve, D. N., van der Kouwe, A. J. W., Hevelone, N. D., Zaleta, A. K., Rosen, B. R., Fischl, B., Corkin, S., Diana Rosas, H., & Dale, A. M. (2005). Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiology of Aging, 26*(8), 1215-1227.

Samame, C., Martino, D. J., & Strejilevich, S. A. (2012). Social cognition in euthymic bipolar disorder: Systematic review and meta-analytic approach. *Acta*

Psychiatrica Scandinavica, 125(4), 266-280.

Schneider, L. C., & Struening, E. L. (1983). SLOF: A behavioral rating scale for assessing the mentally ill. *Social World Research & Abstracts, 19*(3), 9-21.

Seidenfeld, A. M., Johnson, S. R., Woodburn Cavadel, E., & Izard, C. E. (2014). Theory of mind predicts emotion knowledge development in Head Start children. *Early Education and Development, 25*(7), 933-948.

Sergi, M. J., Rassovsky, Y., Nuechterlein, K. H., & Green, M. F. (2006). Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. *American Journal of Psychiatry, 163*(3), 448-454.

Sergi, M. J., Rassovsky, Y., Widmark, C., Reist, C., Erhart, S., Braff, D. L., Marder, S. R., & Green, M. F. (2007). Social cognition in schizophrenia: Relationships with neurocognition and negative symptoms. *Schizophrenia Research, 90*(1-3), 316-324.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., Bennister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation in FSL. *NeuroImage, 23,* Supplement 1:S208-19. doi: 10.1016/j.neuroimage.2004.07.051.

Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: Addressing problems in smoothing, threshold dependence and localization in cluster inference. *Neuroimage, 44*(1), 83-89.

Spreen, O., & Strauss, E. (2006). *A compendium of neuropsychological tests:*

Administration, norms, and commentary. Oxford University Press, USA.

Sukstanskii, A. L., Yablonskiy, D. A., & Ackerman, J. J. (2004). Effects of permeable boundaries on the diffusion-attenuated MR signal: insights from a one-dimensional model. *Journal of Magnetic Resonance, 170*(1), 56-66.

Tuch, D. S. (2004). Q-ball imaging. *Magnetic Resonance in Medicine, 52*(6), 1358-1372.

Tuch, D. S., Reese, T. G., Wiegell, M. R., Wedeen, V. J. (2003). Diffusion MRI of complex neural architecture. *Neuron, 40*(5), 885-895.

Uranova, N. A., Vostrikov, V. M., Orlovskaya, D. D., & Rachmanova, V. I. (2004). Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: A study from the Stanley Neuropathology Consortium. *Schizophrenia Research, 67*(2-3), 269-275.

van Os, J., Kenis, G., & Rutten, B. P. F. (2010). The environment of schizophrenia. *Nature, 468*(7321), 203-212.

Van Overwalle, F. (2009). Social cognition and the brain: A meta-analysis. *Human Brain Mapping, 30*(3), 829-858.

Veenith, T. V., Carter, E., Grossac, J., Newcombe, V. F. J., Outtrim, J. G., Lupson, V., Williams, G. B., Menon, D. K., & Coles, J. P. (2013). Inter subject variability and reproducibility of diffusion tensor imaging within and between different imaging sessions. *PLoS One, 8*(6), doi.org/10.1371/journal.pone.0065941.

Velligan, D. I., Mahurin, R. K., Diamond, P. L., Hazleton, B. C., Eckert, S. L., & Miller, A. L. (1997). The functional significance of symptomatology and cognitive function in schizophrenia. *Schizophrenia Research, 25*(1), 21-31.

Ventura, J., Lukoff, D., Nuechterlein, K. H., Liberman, R. P., Green, M., & Shaner, A.

(1993). Appendix 1: Brief Psychiatric Rating Scale (BPRS) Expanded Version (4.0) scales, anchor points and administration manual. *International Journal of Methods in Psychiatric Research, 3,* 227-243.

Von Der Heide, R. J., Skipper, L. M., Klobusicky, E., & Olson, I. R. (2013). Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. *Brain, 136*(6), 1692-1707.

Vuilleumier, P., & Pourtois, G. (2007). Distributed and interactive brain mechanisms during emotion face perception: Evidence from functional neuroimaging. *Neuropsychologia,45*(1), 174-194.

Wakana, S., Jiang, H., Nagae-Poetscher, L. M., van Zijl, P. D., & Mori, S. (2004). Fiber tract-based atlas of human white matter anatomy. *Radiology, 230*(1), 77-87.

Walter, H., Ciaramidaro, A., Adenzato, M., Vasic, N., Ardito, R. B., Erk, S., & Bara, B. G. (2009). Dysfunction of the social brain in schizophrenia is modulated by intention type: An fMRI study. *Social Cognitive and Affective Neuroscience, 4*(2), 166-176.

Wechsler, D. (2001). Wechsler Test of Adult Reading: WTAR. Psychological Corporation.

Weightman, M. J., Air, T. M., & Baune, B. T. (2014). A review of the role of social cognition in major depressive disorder. *Frontiers in Psychiatry, 5*:179*,* doi:10.3389/fpsyt.2014.00179.

Weinberger, D. R., & Wyatt, R. J. (1983). Enlarged cerebral ventricles in schizophrenia. *Psychiatric Annuls, 13*(5), 412-418.

Wu, Y. C., Field, A. S., Duncan, I. D., Samsonov, A. A., Kondo, Y., Tudorascu, D., &

Alexander, A. L. (2011). High b-value and diffusion tensor imaging in canine model of dysmyelination and brain maturation. *NeuroImage, 58*(3), 829-837.

Yoon, B., Shim, Y. S., Lee, K. S., Shon, Y.M., & Yang, D.W. (2008). Region-specific changes of cerebral white matter during normal aging: A diffusion-tensor analysis. *Archives of Gerontology and Geriatrics, 47*(1), 129-138.

Zhao, X., Sui, Y., Yao, J., Lv, Y., Zhang, X., Jin, Z., Chen, L., Zhang, X. (2017). Reduced white matter integrity and facial emotion perception in never-medicated patients with first episode schizophrenia: A diffusion tensor imaging study. *Progress in Neuropsychopharmacology & Biological Psychiatry, 77*, 57-64.