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Social Cognition as a Predictor of Psychotic Symptoms in 22q11.2 Microdeletion Syndrome

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in Psychology

by

Maria Elizabeth Jalbrzikowski

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ABSTRACT OF THE DISSERTATION

Social Cognition as a Predictor of Psychotic Symptoms
in 22q11.2 Microdeletion Syndrome

by

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22q11.2 Microdeletion syndrome (22qDS) is caused by a recurrent genetic mutation associated with a high degree of social impairment, and also represents one of the greatest known genetic risk factors for schizophrenia. This syndrome therefore represents an excellent model for investigating how a known genetic "lesion" may lead to abnormal development of social behavior and to the expression of a diagnosable psychotic disorder. However, little is known about vulnerabilities that contribute to the development of psychosis in this population, nor have the neurobiological substrates of social cognitive impairment been explored in 22qDS. The present investigation sought to examine social cognitive risk factors, at the level of both behavior and neuroanatomy, which may contribute to psychotic symptomatology in adolescents and young adults with 22qDS.

We conducted three separate studies to investigate these questions. In the first study (22qDS= 31, controls=31), using behavioral measures, we sought to determine whether social cognition better predicts positive symptoms than does non-social cognition in 22qDS. The primary aims of study 2 (22qDS=31, controls= 34) were: 1) to investigate neuroanatomic alterations in socially relevant brain regions (i.e., amygdala, fusiform gyrus, superior temporal gyrus, insula, anterior cingulate, and frontal regions), using structural magnetic resonance imaging (sMRI); and 2) to determine whether such alterations were associated with psychotic symptoms and social cognition in 22qDS patients. Finally, in study 3 (22qDS=26, controls=23), we used diffusion tensor imaging (DTI) to: 1) examine alterations in white matter tracts connecting these 'social brain' regions in 22qDS patients relative to typically developing youth, and 2) to determine whether white matter microstructural abnormalities were associated with psychotic symptoms and social cognition in 22qDS patients.

Several novel findings emerged from these studies. First, in study 1, we found that Theory of Mind (ToM) performance was the best predictor of positive symptoms in 22qDS, accounting for 39% of the variance in symptom severity. In study 2, in comparison to typically developing controls, 22qDS participants showed disruptions in multiple brain regions associated with social cognition. In particular, those with 22qDS had increased cortical volumes in bilateral orbitofrontal cortices and insula, which appeared to be driven by increased cortical thickness in these regions, and decreased cortical volume in bilateral fusiform gyrus and anterior cingulate, which appeared to be driven by decreased surface area in these regions. We also found that increased cortical thickness in the right medial orbitofrontal cortex was significantly associated with increased positive symptom severity in 22qDS, while increased right amygdala volumes were associated with better social cognition performance in 22qDS. Finally, in study 3, in

comparison to typically developing controls, 22qDS participants showed reduced white matter integrity in the left inferior frontal fasciculus and right uncinate fasciculus, fiber tracts that connect occipital to the temporal lobes and medial temporal with orbitofrontal regions, respectively. 22qDS participants also had significantly decreased axial diffusivity, a putative index of axonal damage, in multiple tracts, including the bilateral inferior and superior longitudinal fasciculus (which connects the parietal to the frontal lobes), and the uncinate fasciculus. Greater severity of positive symptoms was associated with decreased axial diffusivity in the left inferior frontal fasciculus and right superior longitudinal fasciculus; in contrast, increased axial diffusivity in the left inferior longitudinal fasciculus was associated with better social cognition in 22qDS.

Considering that both social impairment and neuroanatomic abnormalities predate the onset of psychosis in 22qDS, these findings provide novel information about the relationship between social cognition and psychosis risk in 22qDS. Importantly, study 2 is the first to investigate multiple measures of structural neuroanatomy (i.e., volume, cortical thickness, surface area) in 22qDS and provides important information about functionally distinct subcomponents that may contribute to alterations in cortical volume in social relevant neuroanatomic regions. Also, when testing the joint contribution of behavioral and neuroanatomic measures to prediction of positive symptoms in 22qDS, we found that right medial orbitofrontal cortical thickness and ToM task performance accounted for 43% of the variance in positive symptoms in 22qDS, significantly improving the prediction of positive symptoms in comparison to the ToM behavioral measure alone. Study 3 represents one of the first investigations of multiple DTI indices (i.e., fractional anisotropy, axial and radial diffusivity) in 22qDS. Our pattern of results suggests that white matter microstructural

disruption in 22qDS may be driven by axonal damage, rather than demyelination. Finally, given that ToM was a robust predictor of positive symptoms in our sample and exploratory analyses found relationships between positive symptoms and neuroanatomic regions associated with social cognition in 22qDS, these findings suggest that social cognition may be a valuable intermediate trait for predicting the development of psychosis.

The dissertation of Maria Elizabeth Jalbrzikowski is approved.

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TABLE OF CONTENTS

I. Introduction 1

II. Study 1: Social Cognition in 22q11.2 Microdeletion Syndrome: Relevance to Psychosis? 14

III. Study 2: Are Abnormalities in Social Cognitive Neural Circuitry Related to Psychotic Symptoms in 22q11.2 Microdeletion Syndrome? 43

IV. Study 3: White Matter Integrity as a Predictor of Psychotic Symptoms in 22q11.2 Microdeletion Syndrome 74

V. References 107

LIST OF TABLES

Study 1

Table 1: Demographic and Clinical Characteristics of Study Participants 33

Table 2: Mean raw score for non-social and social cognition measures for 22q11.2 participants and healthy controls. 34

Table 3: Correlation coefficients of age and non-social and social cognition measures in 22q11.2 participants and healthy controls. 35

Table 4: Exploratory Analyses for Social Cognition Measures in 22q11.2 Microdeletion Syndrome vs. Typically Developing Controls 36

Table 5: Predictors of Positive Symptoms in Patients with 22q11.2 Microdeletion Syndrome 37

Table 6: Predictors of Negative Symptoms in Patients with 22q11.2 Microdeletion Syndrome 38

Supplementary Table 1: Correlation values of global IQ and social cognition measures in 22q11.2 participants and healthy controls. 40

Supplementary Table 2: Non-social and social cognition predictors of positive symptoms in 22q11.2 Microdeletion Syndrome, participants prescribed antipsychotics removed from analyses 41

Supplementary Table 3: Non-social and social cognition predictors of negative symptoms in 22q11.2 Microdeletion Syndrome, participants prescribed antipsychotics removed from analyses 42

Study 2

Table 1: Demographic and Clinical Characteristics of Study Participants 67

Table 2: Structural Magnetic Resonance imaging results of neuroanatomic measures associated with social cognition in 22q11.2 deletion participants versus typically developing controls. 68

Supplemental Table 1: Structural Magnetic Resonance imaging results testing for scanner differences. 73

Study 3

Table 1: Demographic and Clinical Characteristics of Study Participants 97

Table 2: Diffusion tensor imaging results for white matter tracts associated with social cognition in participants with 22q11.2 deletion syndrome versus typically developing controls. 98

Supplementary Table 1: Scanner differences in measures of fractional anisotropy, axial diffusivity, and radial diffusivity. 104

LIST OF FIGURES

Introduction

Figure 1: Examining a cognitive phenotype from multiple levels of analysis. 13

Study 1

Figure 1: Performance across non-social and social cognitive domains in 22q11.2 microdeletion syndrome. 39

Study 2

Figure 1: Neuroanatomic regions of interest typically associated with social cognition examined in this study. 69

Figure 2: Developmental disruption in cortical thickness in 22q11.2 Microdeletion Syndrome vs. typically developing controls in the fusiform area and occipital cortex. 70

Figure 3: Relationships between the right amygdala and social cognition measures in 22q11.2 Microdeletion Syndrome. 71

Figure 4: Relationships between the medial orbitofrontal cortices and positive symptoms in 22q11.2 Microdeletion Syndrome 72

Study 3

Figure 1: White matter pathways connecting neuroanatomic structures involved in social cognition examined in this study. 99

Figure 2: Group differences between individuals with 22q11.2 Microdeletion Syndrome versus typically developing controls on measures of fractional anisotropy. 100

Figure 3: Group differences between individuals with 22q11.2 Microdeletion 101

Syndrome versus typically developing controls on measures of axial diffusivity.

Figure 4: Relationships between axial diffusivity in the left inferior longitudinal fasciculus and right superior longitudinal fasciculus and positive symptoms in 22q11.2 microdeletion syndrome. 102

Figure 5: Relationships between axial diffusivity in the left inferior longitudinal fasciculus and social cognition task performance in 22q11.2 microdeletion syndrome. 103

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Study 1 is a version of Jalbrzikowski M, Carter C, Senturk D, Chow C, Hopkins JM, Green MF, Galvan A, Cannon TD, Bearden CE. Social cognition in 22q11.2 microdeletion syndrome: relevance to psychosis? *Schizophrenia Research,* 2012;142(1-3):99-107.

Dr. Bearden is the principal investigator and designed the overall study; Ms. Jalbrzikowski conceptualized the research question for this particular component of the larger study. Ms. Chow wrote and submitted the Internal Review Board protocol for this study, collected and entered data, and provided feedback on drafts of this article. Ms. Hopkins collected and entered data and provided feedback on drafts of this article. Ms. Jalbrzikowski collected and entered the data, managed the literature searches, conducted the statistical analyses, and wrote the article. Ms. Carter assisted in data entry, literature searches, and statistical analyses. Dr. Senturk provided consultation and guidance on the statistical analyses and provided feedback on drafts of this article. Dr. Bearden assisted in writing the manuscript. Dr. Bearden, Dr. Galván, Dr. Green, and Dr. Cannon assisted in conceptualizing the research question, interpreting statistical analyses and provided feedback on drafts of this article. All authors contributed to and have approved the final manuscript.

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Introduction

A considerable research effort has been devoted to searching for the genetic basis of schizophrenia. Though this disorder is highly heritable, the search has been a challenging process, with the consensus arising that neuropsychiatric disorders such as schizophrenia are likely to result from multiple genes interacting with environmental factors to increase one's likelihood for developing the disorder (Bearden, et al., 2008; Cannon & Keller, 2006). Heterogeneity in clinical presentation is a major obstacle in making progress towards discovery of the underlying genetic basis of a behaviorally defined disorder such as schizophrenia (Bearden et al., 2008). Furthermore, the variability in phenotypic presentation may reflect the varied developmental pathways from which the psychiatric syndrome arose.

A complementary strategy that may help us better understand the pathogenesis of schizophrenia is to examine a genetic disorder with a well-defined etiological pathway. 22q11.2 deletion syndrome (Velocardiofacial/DiGeorge syndrome; 22qDS) is a neurogenetic syndrome considered to be among one of the most common known genetic risk factors for the development of psychosis (Bassett, et al., 2003). 22qDS is caused by a hemizygous deletion at chromosome 22q11.2, an area that encompasses approximately 40 genes, including some known to play a role in neuronal migration, myelination and brain development (Maynard, et al., 2003). The extraordinarily high rate of psychotic illness in this group (approximately 30%, Gothelf et al., 2007) offers the possibility of delineating a relatively homogenous developmental pathway to psychosis. This disorder accounts for about 1-2% of schizophrenia cases in the general population (Bassett, et al., 2010). A well defined neurogenetic syndrome like 22qDS can serve as a compelling model to help us understand how abnormal neurodevelopmental processes, which

lead to brain dysfunction, can manifest in disturbances in behavior that are then related to clinical symptoms associated with schizophrenia.

Background on 22qDS

22qDS is the second most common neurogenetic disorder, affecting approximately 1 in 4000 births (Goodship, Cross, LiLing, & Wren, 1998). The 22q11.2 microdeletions range from 1-3 megabases (Mb) in size (Edelmann, et al., 1999; Shaikh, et al., 2000), though thus far there is no evidence that the size of the deletion affects the phenotype severity (Carlson, et al., 1997). The disorder is most frequently caused by a de novo mutation, although approximately 10% of the cases are inherited from parents (Demczuk & Aurias, 1995). While the phenotype of this disorder is highly variable, there are some physical characteristics that are commonly seen in individuals with 22qDS, including craniofacial anomalies, cardiovascular abnormalities, and immune deficiency (Lindsay, 2001; McDonald-McGinn, et al., 1997; Robin & Shprintzen, 2005). 22qDS is also distinguished by a characteristic neurocognitive profile: individuals with 22qDS show visuospatial deficits relative to their verbal performance, and often have lower than average full-scale IQ (Bearden, Woodin, Wang, Moss, McDonald-McGinn, Zackai, Emannuel, et al., 2001; Moss, et al., 1999).

During childhood, 22qDS is linked to an increased rate of neuropsychiatric disorders, such as attention-deficit hyperactivity disorder (ADHD) (1/3 to 1/2 of 22qDS children), anxiety disorders (10-50%), and autism spectrum disorders (14-40%) (Antshel, et al., 2006; Feinstein, Eliez, Blasey, & Reiss, 2002; Fine, et al., 2005). However, it has been hypothesized that these diagnoses represent nonspecific expressions of factors contributing to brain development, particularly since schizophrenia is the only neuropsychiatric disorder shown to have a specific genetic link with 22q11.2 region (Karayiorgou et al., 2010). For example, in gene association

studies involving cases of idiopathic schizophrenia vs. controls, genes within the 22q11.2 region have been associated with schizophrenia (Jungerius, et al., 2008; Williams, et al., 2008). Additionally, 22q11 is one of only two regions supported by two major meta-analyses of schizophrenia linkage studies (Badner & Gershon, 2002; Lewis, et al., 2003). Taken together, these findings provide compelling evidence that 22qDS represents an identifiable genetic subtype of schizophrenia.

Nevertheless, it is still unknown why only one third of the individuals with 22qDS develop a psychotic disorder and the others do not. The overall aim of this dissertation is to identify quantitative, observable factors that indicate an increased risk for developing schizophrenia in 22qDS. Schizophrenia may be best conceptualized as a cluster of quantitative traits that reflect intermediate phenotypes between predisposing genes and syndromal expression (e.g., Gottesman & Gould, 2003). Therefore, investigation of these intermediate traits, or "endophenotypes," and how they relate to psychotic symptoms may be more informative. To understand the most promising risk factors associated with psychosis in 22qDS, we plan to use "deep phenotyping" and explore this genomic variant at multiple levels of analyses (e.g., neural systems, intermediate phenotype, see Figure 1). In particular, we propose to examine behavioral and neuroanatomic measures of social cognition in 22qDS. Considering that social impairment is a key feature of schizophrenia (American Psychiatric Association [*DSM-IV-TR*], 2000) and that greater social impairment has been shown to contribute uniquely to the prediction of psychosis in clinically at-risk adolescents and young adults (Cannon, et al., 2008), variability in social cognition may be a valuable endophenotype for identifying those who convert to a psychotic disorder. However, it is first important to review how social cognition plays a central role in schizophrenia.

Social Cognition in Schizophrenia

Schizophrenia patients have difficulty making accurate judgments about the emotional states of others, inferring others' intentions, and understanding assumptions about relationships between people (Green et al., 2008). These mental operations are broadly defined as social cognition, i.e. how humans understand how other people perceive and think about themselves and how they interpret and respond to others' behavior (Adolphs, 2001). In schizophrenia, both cross-sectional and longitudinal studies have consistently shown that laboratory tasks of social cognition are related to and/or predictive of real-world social functioning (Barnes, et al., 2008; Couture, Penn, & Roberts, 2006). These deficits are also believed to be present prior to the onset of illness (Addington, Penn, Woods, Addington, & Perkins, 2008; Chung, Kang, Shin, Yoo, & Kwon, 2008) and have shown to be better predictors of social functioning than non-social cognition in schizophrenia patients (Sergi, Rassovsky, Nuechterlein, & Green, 2006). Taken together, these findings suggest that social cognition impairments may be central to the pathophysiology of schizophrenia.

Social cognition is a broad concept that encompasses many factors. A 2008 National Institute of Mental Health (NIMH) workshop identified five domains of social cognition that are important to examine in schizophrenia: theory of mind (ToM), social perception, social knowledge, attribution style, and emotion processing (Green, et al., 2008). In this project, we focused on two domains of social cognition: emotion processing and ToM. ToM refers to the ability to comprehend the intentions of others (Frith & Corcoran, 1996) and has been tested with a variety of verbal and visual tasks (e.g., Corcoran, Mercer, & Frith, 1995; Perner & Wimmer, 1985). Impairments across a range of ToM measures have been shown in schizophrenia patients, with strong effect sizes ranging from .90 to 1.25 (Bora, Yucel, & Pantelis, 2009). Furthermore,

ToM deficits have been identified in first-episode (Bertrand, Sutton, Achim, Malla, & Lepage, 2007; Inoue, et al., 2006), chronic (Kern, et al., 2008), and remitted schizophrenia patients (Herold, Tenyi, Lenard, & Trixler, 2002).

Emotion processing refers to the capacity to identify or discriminate between different emotions. Emotion identification tasks typically require the subject to choose an emotion label that best captures the expression on the presented face, whereas emotion differentiation tasks normally involve making a decision about the differences in emotional expression between two stimuli (Erwin, et al., 1992; Kohler, Bilker, Hagendoorn, Gur, & Gur, 2000). When the initial studies showing emotion identification impairment in schizophrenia were published, some researchers hypothesized that that these impairments occurred because the patients did not comprehend the labels used to identify emotions, not due to an inability to recognize the emotion, particularly since others showed that schizophrenia patients performed worse on labeling tasks in comparison to matching tasks (e.g., Mandal & Palchoudury, 1985). Therefore, emotion differentiation tasks were also created (e.g., Kerr & Neale, 1993). However, regardless of task type, impairment in tasks of both emotion identification and differentiation has consistently been observed in first-episode, chronic, and remitted adult patients with schizophrenia, with an average effect size of .91 (Kohler, Walker, Martin, Healey, & Moberg, 2010). First-degree relatives of schizophrenia patients show intermediate levels of impairment on tasks of ToM and emotion processing (Gur et al., 2007; Irani et al., 2006). Furthermore, significant heritability estimates for measures of emotion processing have been identified (Greenwood et al., 2007). Collectively, this evidence suggests that these two constructs of social cognition may be promising endophenotypes to pursue in schizophrenia research. Additionally, due to the fact that a large body of basic research exists for clinical researchers to build upon,

Ochsner (2008) reviewed and highlighted emotion processing and ToM as two domains of social cognition with the most potential for translational research. Existing findings regarding the neural bases of normal human social cognition offer a framework to better understand how these constructs are affected and/or disrupted in schizophrenia.

Social Deficits in 22qDS

Understanding whether social cognition deficits in genetic high-risk groups predict psychotic symptoms may help identify potential endophenotypes associated with schizophrenia. Although social impairment has been repeatedly identified via parental report in 22qDS individuals (Kiley-Brabeck & Sobin, 2006; Swillen, et al., 1997; Woodin, et al., 2001), the literature on 22qDS and social cognition offers only preliminary findings. On an emotion identification task, adolescents with 22qDS displayed significant impairment in detecting anger, fear, and disgust in comparison to healthy controls, but their ability to recognize happy, neutral, and surprise was preserved (Campbell et al., 2010). Additionally, 22qDS adults with a diagnosis of schizophrenia have shown ToM impairments in comparison to non-psychotic 22qDS individuals, suggesting a similar pattern of social cognitive deficit to that observed in idiopathic schizophrenia; however, this study did not examine adolescents, nor was a healthy comparison group included (Chow, Watson, Young, & Bassett, 2006). Recent evidence suggests that, in comparison to typically developing controls, those with 22qDS show impairment in making mental state attributions and this deficit is related to real world social impairment in those with 22qDS (Ho, et al., 2012).

Based on these initial findings, and because social cognition deficits may represent a core feature of schizophrenia, we first examined social cognitive task performance as a predictor of psychotic symptoms in 22qDS. In this first study, we used objective measures of nonsocial and

social cognition and examine which of these best predicts psychotic symptoms, as measured by the Structured Interview for Prodromal Symptoms (SIPS, McGlashan et al., 2001). The SIPS has shown to be a valid and reliable measure that is highly predictive of future psychotic disorder diagnoses (Cannon et al., 2008; Woods et al., 2009). Considering that psychotic symptoms are thought to be on a continuum with fully psychotic traits, we believe it is more appropriate to use a continuous symptom measure to understand prediction in relation to risk for progression and increasing severity of illness, as opposed to risk for categorical diagnosis of illness.

Social Cognition and Adolescence

In addition, in this first study we also examined how the developmental trajectory of social cognition may be disrupted in adolescents and young adults with 22qDS. In regards to the social environment, adolescence is a significant period of time for the growth of one's identity and for understanding oneself in relation to others (Blakemore & Choudury, 2006). During adolescence, young people become more concerned with how they are seen by others, become more independent in their decision-making processes, and experience important developmental shifts in their relationships. At the same time, the pathophysiology of psychiatric disorders, particularly schizophrenia, is believed to arise from aberrations in brain maturation during adolescence (Paus et al., 2008). Examining how the development of social cognitive skills may be disrupted in 22qDS- as well as how it relates to the development of psychosis- can provide us with valuable insights into how social development is affected by brain dysmaturation during this time period.

In comparison to adults, typically developing adolescents show a qualitatively different pattern of neural engagement during functional neuroimaging tasks of social cognition (Burnett, Bird, Moll, Frith, & Blakemore, 2009; Pfeifer, Lieberman, & Dapretto, 2007). One hypothesis

for this differential involvement is that adolescents are still developing social skills necessary to appropriately interact in interpersonal situations (Burnett & Blakemore, 2009). In this first study, we expected to see that the typical development of social cognitive skills throughout adolescence is disrupted in 22qDS, which may help elucidate how brain dysmaturation plays a role in the link between social cognition and psychotic symptoms.

The Social Brain

According to the neurodevelopmental hypothesis of schizophrenia, the typical onset of illness during late adolescence is likely related to widespread maturational changes that occur in the brain during this time period (McGlashan & Hoffman, 2000). As the brain matures through adolescence, there is an increase in white matter in the prefrontal cortex, which reflects increased myelination and is thought to improve the effectiveness of neural transmission (Giedd, et al., 1999; Paus, 2005). Concomitantly, due to the synaptic pruning that takes place, there is a decrease in synaptic density, as measured by a decrement in gray matter volume (Sowell, et al., 2003). These developmental changes in brain structure may mediate the development of social cognition in adolescents, particularly in regards to the differential levels of maturity in the subcortical vs. cortical areas of the brain (Casey et. al., 2008).

Many of the structural neuroanatomic changes that take place during adolescence occur in areas of the brain implicated in social cognition (Blakemore, 2008b). Though a large network of brain regions is likely involved in processing social information, brain areas consistently associated with social cognition include the medial prefrontal cortex (mPFC), anterior cingulate (ACC), amygdala, and superior temporal sulcus (STS) (Blakemore & Choudhury, 2006; Lieberman, 2007; Ochsner, 2008). Longitudinal studies of healthy adolescents have identified progressive gray matter decreases in the prefrontal cortex, ACC, and STS (Barnea-Goraly, et al.,

2005; Gogtay, et al., 2004; Sowell, et al., 2003; Sowell, Thompson, Tessner, & Toga, 2001). These findings suggest that there is a link between the social behavior changes and normal brain maturational changes seen during adolescence.

Structural Magnetic Resonance Imaging, Social Cognition, and Psychosis

Research suggests that those at clinical high risk for psychotic illness have abnormalities in neuroanatomic regions associated with social cognition. Longitudinal studies have found progressive volume decreases in superior temporal and prefrontal regions, in clinical high risk individuals who go on to convert to psychosis (Borgwardt, et al., 2007; Pantelis, et al., 2003; Sun, et al., 2009; Takahashi et al., 2009). Congruent with this literature, in a study of 22qDSchildren children, Bearden et al. (2004) found that reduced temporal gray matter was associated with severity of Thought Problems (as measured by the Child Behavior Checklist) in non-psychotic youth with 22qDS. Notably, Kates et al. (2011) found that in 22qDS individuals, decreases in the superior temporal gyrus predict positive symptoms at follow-up. Taken together, these findings suggest that common biological mechanisms may underlie social cognitive impairments and psychosis.

As such, the second study of my dissertation project was to examine whether structural alteration in brain regions associated with social cognition is linked with psychotic symptom development and/or social cognition performance in 22qDS individuals. We assessed gray matter volume, cortical thickness, and surface area of key brain regions comprising the social cognitive network (i.e., amygdala, fusiform gyrus, superior temporal gyrus, insula, anterior cingulate, superior frontal cortex, middle frontal cortex, and inferior frontal cortex) and examined relationships between these regions and positive symptoms and social cognition performance in 22qDS. We also tested whether the joint contribution of behavioral and

neuroanatomic measures improved prediction of positive symptoms in 22qDS. Finally, we sought to identify whether there was an altered age-related trajectory of these brain regions in 22qDS.

Diffusion Tensor Imaging, Social Cognition, and Psychosis

White matter tracts connecting nodes of the "social cognitive brain network" are also likely to play an important role. A relatively new imaging technique, known as diffusion tensor imaging (DTI), looks at the diffusion of water to investigate organization of white matter tracts. Greater diffusion in one direction (anisotropic diffusion) suggests the existence of barriers, such as axonal tracts. The most commonly used measure in DTI is fractional anisotropy (FA) and reduced FA suggests abnormalities of white matter integrity. Reduced FA in the superior longitudinal fasciculus, which connects frontal, occipital, parietal, and temporal lobes, has been found in clinically ascertained high-risk individuals (Karlsgodt, Niendam, Bearden, & Cannon, 2009). Similarly, two other DTI studies found reduced connectivity in the superior longitudinal fasciculus in 22qDS individuals (Sundram, et al., 2010) (Barnea-Goraly, et al., 2003). Disruption of the development of white matter integrity may contribute to both social cognitive impairment and psychosis.

Collectively, these results suggest that the social-cognitive impairments hypothesized to be relevant to psychotic symptom development in 22qDS may be driven by absence of – or poorly synchronized – "long distance" connectivity between these brain areas. How these processes develop – or fail to appropriately develop – during adolescence is not well understood. It has long been proposed that schizophrenia is a disorder of "dysconnectivity," with early brain vulnerabilities such as disruption of white matter integrity (Davis, et al., 2003) affecting later developmental processes in the brain. It has been suggested that these disruptions likely occur as

a consequence of disruption in genes involved in neurodevelopment (Walsh, et al., 2008). For that reason, examining the white matter microstructure connecting brain regions associated with social cognition (a complex construct requiring the use of interconnected brain regions), and its contribution to the prediction of psychotic symptoms in a genetically homogenous subset of individuals at high-risk for the disorder may better elucidate neurobiological mechanisms underlying the development of psychosis.

Thus, the third aim of this dissertation was to examine white matter integrity in tracts connecting "social cognitive" regions (i.e., superior longitudinal fasciculus, uncinate fasciculus, anterior cingulum, inferior longitudinal fasciculus, and inferior frontal occipital fasciculus) through the use of diffusion tensor imaging (DTI) in 22qDS individuals. We then explored relationships between DTI measures, social cognition task performance and positive symptoms of psychosis in 22qDS and sought to identify whether there is an altered age-related trajectory of these white matter pathways in 22qDS.

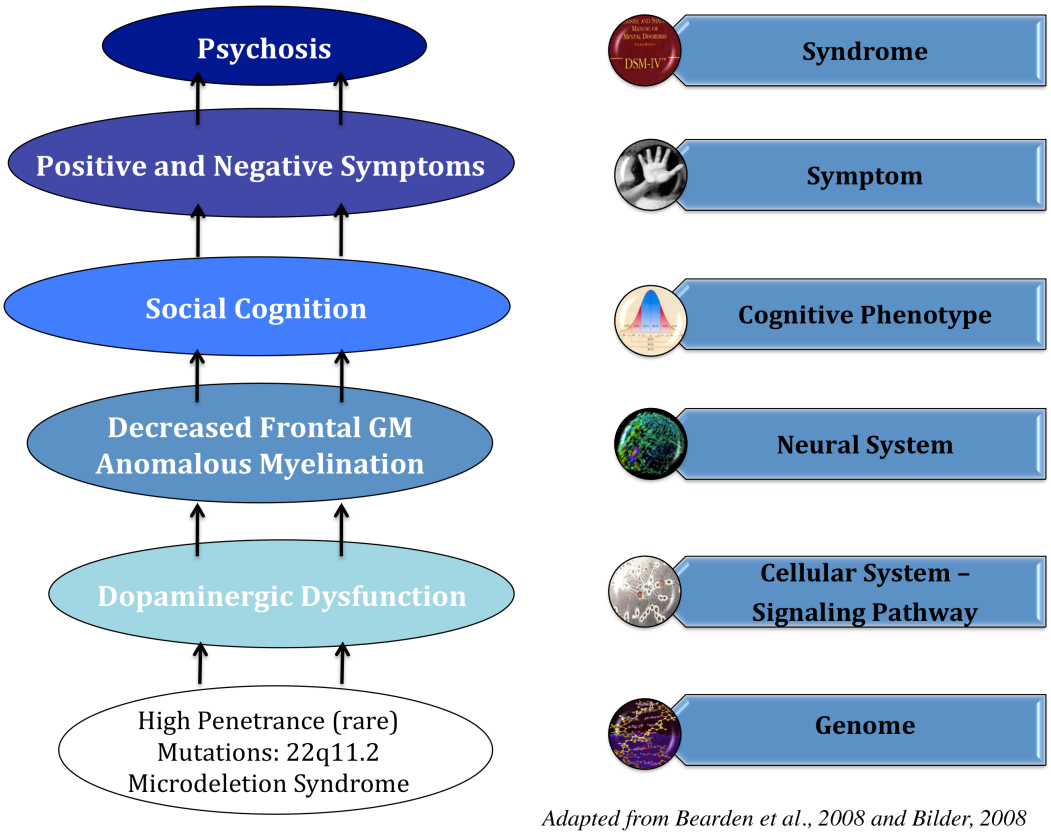
Conclusion

The specific aims of this dissertation project are: 1) To examine the ability of social cognition tasks to predict psychotic symptoms in 22qDS adolescents and young adults, 2) to explore whether structural variation in brain areas associated with social cognition is associated with psychotic symptoms and/or social cognition performance in those with 22q11.2 deletion syndrome, 3) to identify if disruption in white matter tracts associated with social cognition in 22qDS individuals is related in psychotic symptoms and/or social cognition performance and 4) to observe whether those with 22qDS show age-related developmental disruptions in social cognition performance, structural brain areas associated with social cognition, and white matter tracts linking brain regions associated with social cognition. A future direction for this research

is to investigate whether baseline social cognition performance predicts progressive structural brain changes in the medial prefrontal cortex, anterior cingulate cortex, and/or superior temporal sulcus over time in individuals at high risk for developing schizophrenia. The findings from this study will also provide a foundation for future longitudinal studies further exploring the development of brain maturation and social cognitive abilities in both healthy adolescents and those at high risk for developing schizophrenia.

Introduction: Figures

Figure 1: Examining A Cognitive Phenotype From Multiple Levels of Analysis (Adapted from Bearden et al., 2008 & Builder et al., 2008)



Adapted from Bearden et al., 2008 and Bilder, 2008

Social Cognition in 22q11.2 Microdeletion Syndrome: Relevance to Psychosis?

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Abstract

22q11.2 deletion syndrome (22qDS) represents one of the largest known genetic risk factors for schizophrenia. Approximately 30% of individuals with 22qDS develop psychotic illness in adolescence or young adulthood. Given that deficits in social cognition are increasingly viewed as a central aspect of idiopathic schizophrenia, we sought to investigate abilities in this domain as a predictor of psychotic symptoms in 22qDS participants. We assessed multiple domains of social and non-social cognition in 22qDS youth to: 1) characterize performance across these domains in 22qDS, and identify whether 22qDS participants fail to show expected patterns of age-related improvements on these tasks; and 2) determine whether social cognition better predicts positive and negative symptoms than does non-social cognition. Task domains assessed were: emotion recognition and differentiation, Theory of Mind (ToM), verbal knowledge, visuospatial skills, working memory, and processing speed. Positive and negative symptoms were measured using scores obtained from the Structured Interview for Prodromal Symptoms (SIPS). 22qDS participants (N=31, mean age: 15.9) showed the largest impairment, relative to healthy controls (N=31, mean age: 15.6), on measures of ToM and processing speed. In contrast to controls, 22qDS participants did not show age-related improvements on measures of working memory and verbal knowledge. Notably, ToM performance was the best predictor of positive symptoms in 22qDS, accounting for 39% of the variance in symptom severity. Processing speed emerged as the best predictor of negative symptoms, accounting for 37% of the variance in symptoms. Given that ToM was a robust predictor of positive symptoms in our sample, these findings suggest that social cognition may be a valuable intermediate trait for predicting the development of psychosis.

1. Introduction

The 22q11.2 deletion syndrome (Velocardiofacial/DiGeorge syndrome; 22qDS) is a neurogenetic disorder resulting from a hemizygous deletion at chromosome 22q11.2. Approximately 30% of individuals with 22qDS develop a psychotic disorder in adolescence or early adulthood (Gothelf, Feinstein, et al., 2007), making this syndrome one of the largest known genetic risk factors for schizophrenia (Karayiorgou, Simon, & Gogos, 2010). 22q11.2 deletions account for about 1-2% of schizophrenia cases in the general population (Bassett, et al., 2010). Moreover, schizophrenia patients with 22qDS have clinical profiles that are indistinguishable from schizophrenia patients without the deletion (Bassett, et al., 2003; Murphy, Jones, & Owen, 1999). Well-defined genetic subtypes of neuropsychiatric disorders like 22qDS – with a known, homogeneous etiology – may be informative for developing and understanding the pathophysiology of schizophrenia in the broader population (Bearden, et al., 2008). However, there is wide variability in the phenotype associated with 22qDS, and it is not known why only a certain percentage of individuals with the microdeletion develop psychosis.

Social cognition has been identified as a potential endophenotype, or intermediate trait, that functions as a marker of psychosis vulnerability (Penn, Sanna, & Roberts, 2008). Endophenotypes are quantifiable traits hypothesized to relate more directly to the underlying genes and neural circuitry disturbances than the heterogeneous symptom clusters associated with psychiatric syndromes (Gottesman & Gould, 2003). Social cognitive deficits have been consistently found in individuals with schizophrenia across a range of measures (e.g., Corrigan & Toomey, 1995; M. F. Green, et al.; Inoue, et al., 2006; Kohler, et al., 2000). Particularly marked deficits have been identified in the domains of emotion processing (i.e., the ability of

schizophrenia patients to recognize the affective state of others; effect size=.91; Kohler, et al., 2010), and the capacity to understand the intentions of others, or theory of mind (ToM, effect size ranging from .90 to 1.25; Bora, Yucel, & Pantelis, 2009). Impairments in ToM and emotion processing have been identified in first-episode and chronic patients with schizophrenia, in acute and remitted phases of the illness (Bediou, et al., 2005; Gessler, Cutting, Frith, & Weinman, 1989; Herbener, Hill, Marvin, & Sweeney, 2005; Novic, Luchins, & Perline, 1984), as well as in the prodromal period (M. F. Green, et al., 2011), suggesting that these are stable deficits across phases of illness. Additionally, the majority of studies report that first-degree relatives of schizophrenia patients show intermediate levels of impairment on tasks of ToM and emotion processing (Eack, et al., 2010; Gur, Nimgaonkar, et al., 2007; Irani, et al., 2006; Surguladze, et al., 2012); but see also (Bolte & Poustka, 2003; Marjoram, et al., 2006). Finally, in family studies measures of emotion processing have been shown to be significantly heritable (Greenwood, et al., 2007). Collectively, this evidence suggests that these two constructs of social cognition may be promising endophenotypes to investigate in individuals at genetic high risk for schizophrenia, as they could potentially have predictive validity for determining who is most likely to develop the illness.

The profound social dysfunction in schizophrenia, considered to be a hallmark feature of the disorder, has also been observed in individuals with 22qDS (Kiley-Brabeck & Sobin, 2006; Swillen, et al., 1997; Woodin, et al., 2001). In individuals with 22qDS, poor sociability scores on parent-rated questionnaire measures, fewer interests, increased social withdrawal, and poor social functioning have been associated with concurrent psychotic symptoms (Baker & Skuse, 2005; Debbane, Glaser, David, Feinstein, & Eliez, 2006). In comparison to individuals with Williams syndrome (a neurogenetic disorder believed to involve intact emotion processing,

despite marked IQ deficits), 22qDS individuals showed impaired accuracy in emotion recognition (Campbell et al., 2009) and another study by the same research group found that, in comparison to healthy controls, adolescents with 22qDS displayed significant impairment in detecting anger, fear, and disgust on an emotion identification task, but their ability to recognize happy, neutral, and surprised faces was preserved (Campbell et al., 2010). In studies examining theory of mind (ToM) in 22qDS, youth with 22qDS exhibited significant impairments on cognitive ToM tasks (Campbell et al., 2011), while Chow et al. (2006) found that 22qDS adults with a diagnosis of schizophrenia showed significant impairment on a ToM task in comparison to 22qDS individuals without a diagnosis of schizophrenia (effect size=.95). However, the relative contributions of social versus non-social cognitive deficits to the prediction of psychotic symptom severity in 22qDS have yet to be examined.

Additionally, because our sample consists largely of adolescents – a critical period for the emergence of psychotic symptoms – it presents an ideal cohort in which to investigate social cognition within a developmental framework. Adolescence represents a time of particular vulnerability involving large changes in one's social environment (e.g., spending significantly more time with same-aged peers), increasing concern with others' perceptions, and increasing independence (Spear, 2000). In tandem with these changes, the adolescent brain is also undergoing dramatic structural neuroanatomic changes in areas believed to underlie social cognition (Blakemore, 2008b). As such, the second aim of this study is to examine the effects of age on social cognition in 22qDS youth, as compared to healthy adolescents. These findings may be critical for understanding the effects of brain maturation on social cognition in at-risk youth.

Here we examined ToM and emotion processing performance of individuals with 22qDS compared to an age-matched typically developing control sample. We had the following predictions. 1) 22qDS will show deficits, relative to healthy controls, on both emotion processing and ToM tasks. Furthermore, based on prior studies of 22qDS youth (Campbell et al., 2010) and behaviorally defined clinical high-risk (CHR) populations (Amminger, et al., 2011), we hypothesized that those with 22qDS will have relatively greater impairment in the ability to recognize negative emotions. 2) With regard to social cognitive developmental trajectories, age-associated increases in social cognitive abilities will be observed in typically developing adolescents. Although exploratory, we expect this relationship will not be present, or present to a lesser degree, in those with 22qDS, suggesting aberrant processes of brain maturation affecting social cognitive neural circuitry. 3) Within the 22qDS group, social cognition will be associated with positive and negative symptom severity; and secondly, social cognitive measures will explain more of the variance in symptom severity than non-social cognitive measures. .

2. Methods

2.1 Participants

The total sample consisted of 62 participants (10-25 years old, 31 22qDS and 31 controls). 22qDS participants consisted of individuals with a molecularly confirmed diagnosis of 22q11.2 deletion syndrome recruited from an ongoing longitudinal study at the University of California, Los Angeles (UCLA). Healthy controls were recruited from this study and another longitudinal study examining individuals at clinical high-risk for developing psychosis at UCLA. Exclusion criteria for all study participants were: neurological or medical condition disorder that might affect performance, insufficient fluency in English, and/or if they endorsed substance or alcohol

abuse and/or dependence within the past six months. Healthy controls additionally did not meet criteria for any major mental disorder, with the exception of attention deficit–hyperactivity disorder (ADHD) or a past episode of depression, based on information gathered during the Structured Clinical Interview for DSM-IV Axis I Disorders (First, Spitzer, Gibbons, & Williams, 1997).

All participants underwent a verbal and written informed consent process. Participants under the age of 18 years provided written assent, while their parent or guardian completed written consent. The UCLA Institutional Review Board (IRB) approved all study procedures and informed consent documents.

2.2 Measures

2.2.1 Structured Interview for Prodromal Syndromes

A master's level trained clinician assessed all participants on the positive, negative, disorganized, and general symptom scales from the Structured Interview for Prodromal Syndromes (SIPS; McGlashan, 2001). Symptoms on these scales are rated from 0-6, with zero representing an absence of symptoms and six referring to an extremely severe level of symptoms. This measure has shown excellent inter-rater reliability (above .75, Meyer, et al., 2005; Miller, et al., 2003). All raters demonstrated good inter-reliability for symptom ratings, with kappa values ranging from .85 to 1.00. For the purposes of this study, we used the sum of the positive and negative SIPS symptom scores as separate dimensional measures of psychotic symptoms. These measures encompass a range of symptom severity, including sub-threshold (prodromal) and fully psychotic symptoms.

2.2.2 Social Cognition Tasks

Study participants received the Penn Emotion Recognition Test (ER40), a computerized emotion identification task in which 40 color photographs of adult faces, varying in race and gender, are randomly presented (Kohler, et al., 2000). Participants were asked to identify the emotion of each face (happy, sad, anger, fear, or no emotion) and were given as long as needed to respond (total maximum score=40, each emotion presented 8 times). Participants also received the Penn Emotion Differentiation Task (EMODIFF), a computerized emotion differentiation task in which individuals are presented with two black and white faces of the same person and are asked to choose which of the two faces displayed expresses an emotion more intensely (e.g., more happy, more sad), or decide that the two faces are equally happy or sad (total maximum score=40) (Erwin, et al., 1992). Both measures have shown adequate construct validity and test-retest reliability (Carter, Barch, Gur, Pinkham, & Ochsner, 2009; Rojahn, Gerhards, Matlock, & Kroeger, 2000), have been widely used in studies with schizophrenia patients (e.g., Butler, et al., 2009; Sachs, Steger-Wuchse, Kryspin-Exner, Gur, & Katschnig, 2004; Silver, Shlomo, Turner, & Gur, 2002), as well as in adolescents (Roddy, et al., 2012; Schenkel, Pavuluri, Herbener, Harral, & Sweeney, 2007).

All participants were administered Part 3 of The Awareness of Social Inference Test (TASIT, McDonald, Flanagan, Rollins, & Kinch, 2003). The TASIT is a computerized task believed to assess one's ability to comprehend the intentions of others, particularly how one comprehends white lies or sarcasm. The task consists of 16 vignettes (each lasting between 15-60 seconds), eight of which show an individual telling a lie, while the other eight display an interaction in which someone uses sarcasm. After viewing each vignette, an assessor asked the participant four questions related to the scene: 1) what someone is doing to another person in the scene, 2) what someone is trying to say to the other person, 3) what one of the individuals in the

scene is thinking, and 4) what one of the characters in the vignette is feeling. After task completion, an overall score was calculated (maximum=64). The TASIT has shown adequate reliability and validity with brain-injured patients (McDonald, et al., 2006), and has been used with adolescents at clinical high-risk for psychosis, along with first-episode and chronic patients with schizophrenia (M. F. Green, et al., 2011).

2.2.3 Non-Social Cognition Tasks

Supervised clinical psychology doctoral students or Ph.D. staff administered a neuropsychological battery assessing multiple domains of cognitive functioning. The domains of processing speed, working memory, and verbal knowledge were selected because these domains are considered central deficits in schizophrenia and represent potential endophenotypes of the disorder (Dickinson, Ramsey, & Gold, 2007; Gur, Calkins, et al., 2007; Snitz, Macdonald, & Carter, 2006). Visuospatial reasoning was also examined, because 22qDS is typically characterized by relative weakness in visuospatial abilities (Bearden, Woodin, Wang, Moss, McDonald-McGinn, Zackai, Emanuel, et al., 2001). Vocabulary and Matrix Reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) were administered and used as measures of verbal knowledge and visuospatial skills, respectively. Speed of processing was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS) Symbol Coding task (Keefe, et al., 2004) and working memory was assessed with the University of Maryland Letter Number Sequencing (LNS) task (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997).

2.3 Statistical Analyses

All statistical analyses were performed using SPSS software v. 19 (Chicago, Illinois). We compared demographic characteristics between groups using independent samples t-tests for

continuous variables and chi-square tests for categorical variables. One 22qDS individual was unable to complete the ER40 task and was removed from all subsequent analyses. Task data were examined for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests.

For both social and non-social cognition measures, one-way ANOVAs were conducted using the raw score as the dependent variable, group as a fixed factor, and age as a covariate. If an interaction between group and age was not significant, the interaction term was removed from the final model. All main-effects and interactions were followed up with appropriate t-tests or Pearson correlations. To directly compare the strength of correlations between the two groups, a Fisher r-to-z transformation was conducted. Effect sizes for group comparisons were calculated with the Cohen's *d*, which provides a measure of effect size for group differences. Because the distributions of two tasks violated assumptions of normality for the 22qDS group, we also conducted non-parametric Kruskal-Wallis Tests to confirm the one-way ANOVA results.

To identify whether 22qDS participants showed a differential deficit in their ability to recognize specific emotions, we conducted an exploratory repeated-measures ANOVA (rmANOVA; Group x Emotion) with EMODIFF and ER40 tasks. An exploratory rmANOVA was also conducted with the TASIT, to determine whether participants with 22qDS showed differential impairment in detecting lies versus sarcasm.

To examine the relationship between the social and non-social cognitive tasks and clinical symptoms, as assessed by the SIPS interview, in the 22qDS sample, we conducted separate linear regression analyses with each social cognition construct (emotion identification, emotion differentiation, ToM) and each non-social cognition construct (verbal knowledge, visuospatial skills, speed of processing, working memory) as a predictor, age as a covariate, and SIPS symptom scores (total positive and negative symptoms on the SIPS) as the dependent

variables. In a secondary analysis, we re-ran these analyses after removing any individuals who were taking antipsychotic medication at the time of assessment (n=4). To determine whether or not the variance could be better explained by general intellectual abilities, we also included global IQ as a covariate in the models of the two most significant predictors.

To determine whether social or non-social cognition was a stronger predictor of positive and negative symptoms in 22qDS, we then conducted separate linear regression analyses for positive and negative symptoms as the dependent variables, including the most significant social cognition predictor and the most significant non-social cognition predictor, with age as a covariate.

4. Results

As shown in Table 1, 22qDS patient and control groups were matched on all demographic factors (all p-values .08 or greater). Relationships between global IQ and social cognition measures for 22qDS participants and controls are included in Supplementary Table 1.

4.1 Group Comparisons: Non-social and Social Cognition

22qDS participants overall were significantly impaired on all measures, relative to age-matched controls (Figure 1); significant main effects of group were found for visuospatial skills, whereas significant main effects for both age and group were seen for processing speed. Of note, there was a significant Age by Group (22qDS vs. control) interaction for working memory and verbal knowledge measures, although main effects of group were not significant. Controls showed a significant positive relationship between age and working memory performance (r=.75, p<.001), while this relationship was not significant in 22qDS participants (r=.29, p=.12). Fisher's test for the equivalence of correlations showed that the strength of this correlation was significantly greater in controls relative to 22qDS participants (z=2.5, p=.01). For verbal

knowledge, controls showed a significant positive relationship between age and task performance (r=.79, p<.001), as did 22qDS participants (r=.42, p=.02), albeit to a lesser degree. However, the strength of this relationship did not significantly differ in 22qDS vs. controls (z=1.2, p=.13).

For social cognition tasks, ToM, emotion recognition, and emotion differentiation all showed a main effect of group, while only ToM and emotion differentiation showed a significant main effect of age. Controls showed a strong relationship between age and TASIT performance (r=.55, p=.001), with better performance in older participants. This relationship was not significant in 22qDS participants (r=.32, p=.08). Fisher's test for the equivalence of correlations did not show a difference in correlation strength, in controls relative to 22qDS participants (z=1.0, p=.3). Non-parametric Kruskal-Wallis tests conducted on all measures also showed a significant main effect of group (all p-values p<.001).

Mean raw scores, t-tests for equality of means, and effect sizes for all social cognition measures in 22qDS participants and healthy controls are displayed in Table 2. Table 3 displays the correlation coefficients of age and non-social and social cognition measures in both groups, along with the Fisher r-to-z transformations to test for equality of correlations.

4.2 Social Cognition: Exploratory Analyses for Type of Emotion

The results from the rmANOVA for social cognition tasks are presented in Table 4. Of note, there was a significant Group by Emotion interaction for ER40 (F(4,55)=2.6, p=.04). Follow up t-tests revealed that 22qDS participants were significantly impaired, relative to healthy controls, in their ability to detect anger (t=3.1, p=.001), happiness (t=2.8, p=.007), and sadness (t=3.9, p<.001), but not fear (t=0.6, p=.57) or no emotion (t=1.2, p=.25) .

4.3 Predictors of Positive Symptoms in 22qDS

Separate linear regression analyses revealed that 4 out of 7 measures were significant predictors ($p<.05$) of positive symptoms (Table 5). After Bonferroni correction for multiple comparisons ($p=.007$), only ToM remained as a significant predictor ($F(2,27)=8.6$, $p=.001$), accounting for 39% of the variance in positive symptoms. ToM still remained the most significant predictor in a sensitivity analysis, in which the 4 22qDS participants taking antipsychotics were removed ($F(2,24)= 4.0$, $p=.031$ Supplementary Table 2). When global IQ, ToM, and age were all entered as predictors in the regression analysis, the overall model remained significant ($F(3,26)=5.9$, $p=.003$), accounting for 41% of the variance in positive symptoms. Within this model, ToM ($b=-.53$, $p=.02$) remained a significant predictor of positive symptoms, while global IQ ($b=-.18$, $p=.38$) and age ($b=.15$, $p=.39$) were not significant predictors.

When the most significant non-social cognition predictor (processing speed) and social cognition predictor (ToM) were included together as predictors in a linear regression, the overall model was significant ($F(3,26)=6.9$, $p=.001$), with the combination of these predictors accounting for 45% of the variance in positive symptoms. In this model, ToM remained a significant predictor ($b=-.53$, $p=.005$) of positive symptoms in 22qDS, while processing speed was not ($b=-.32$, $p=.11$).

4.4 Predictors of Negative Symptoms in 22qDS

Separate linear regression analyses also revealed that 4 out of 7 measures were significant predictors ($p<.05$) of negative symptoms in the 22qDS group (Table 6). Processing speed was the most significant predictor of negative symptoms in 22qDS ($F(2,27)=8.0$, $p=.002$), accounting for 37% of the variance in negative symptom severity. Emotion recognition and short-term working memory were also significant predictors of negative symptoms in 22qDS ($F(2,27)=4.9$,

p=.02), but these findings did not survive correction for multiple comparisons. When global IQ, processing speed, and age were all entered as predictors in the regression analysis, the overall model remained significant (F(3,26)=5.1, *p*=.006), accounting for 37% of the variance in negative symptoms. Within this model, processing speed (*b*=-.68, *p*=.004) and age (*b*=.62, *p*=.004) emerged as significant predictor of negative symptoms, while effect of global IQ (*b*=.02, *p*=.93) on negative symptoms was not significant.

When the most significant non-social cognition predictor (processing speed) and social cognition predictor (emotion recognition) were included together as predictors in a linear regression analysis, the overall model was significant (F(3,26)=8.5, p<.0001), with the combination of these predictors accounting for 50% of the variance in negative symptoms. Both processing speed (b=-.59, p=.002) and emotion recognition (b=-.36, p=.02) remained significant predictors of negative symptoms.

5. Discussion

The present study examined the ability of social and non-social cognitive measures to predict positive and negative symptoms in adolescents and young adults with 22q11.2 microdeletion syndrome, a neurogenetic disorder considered to be one of the greatest known risk factors for psychosis. Notably, ToM emerged as the best predictor of positive symptoms, accounting for 39% of the variance in symptom severity in those with 22qDS. This finding remained when the most significant non-social cognitive predictor or global IQ were also included as covariates in the regression analysis, suggesting that social cognitive measures uniquely predict positive symptoms, over and above non-social cognition measures. This finding provides preliminary evidence to further explore social cognition measures as candidate endophenotypes for identifying psychosis risk in 22qDS patients.

In comparison to typically developing controls, 22qDS participants exhibited impaired performance on all social and non-social cognition measures. Though all effect sizes were medium to large (Cohen's *d* range: .9-2.3 across measures), we observed that those with 22qDS showed the greatest impairment on tasks of ToM and processing speed. Notably, these two tasks also emerged as the most significant predictors of positive and negative symptoms in 22qDS, respectively. We also identified differential effects of age for both working memory and verbal knowledge (Vocabulary), in 22qDS participants vs. controls, with control subjects showing greater age-related increases in task performance. In addition, controls showed a significantly stronger linear relationship between working memory and age, suggesting there may be a disrupted trajectory of the development of working memory abilities in 22qDS. These findings suggest that as youth with 22qDS get older, they do not continue to improve in their working memory abilities, as typically developing youth do (Waber, Forbes, Almli, & Blood, 2012). More specifically, our results suggest that youth with 22qDS start with impairments in working memory abilities, but as they progress through adolescence, this impairment becomes greater. This disruption could reflect an aberrant neurodevelopment trajectory in the neural circuits that support working memory performance in 22qDS. However, this intriguing cross-sectional finding should be validated with within-subject longitudinal data.

Our results complement and extend up on those of previous studies examining social cognition and social behavior in 22qDS. Chow et al. (2006) showed that, in comparison to adults with 22qDS without schizophrenia, 22qDS individuals with a diagnosis of schizophrenia showed significant impairment on a ToM task. In fact, when compared with other neurocognitive measures, the effect size for ToM differences was one of the largest between these two groups. Others have found that lower scores on parent-reported sociability, peer relations, and interests,

were significantly correlated with higher levels of schizotypy symptoms (Baker & Skuse, 2005). Youth with 22qDS and psychotic symptoms also have more social withdrawal and less adaptive socialization skills in comparison to 22qDS youth without psychotic symptoms (Debbane, et al., 2006). Collectively, these findings provide evidence that both laboratory measures of social cognition and real-world social behavior are highly relevant to psychosis risk in 22qDS.

It should be noted that non-social neurocognitive measures, such as verbal knowledge and processing speed, were also significant predictors of positive symptoms in our sample. Furthermore, a decline in verbal IQ (Gothelf, Penniman, Gu, Eliez, & Reiss, 2007; Kates, Antshel, et al., 2011) and impairments in executive functioning (Antshel, et al., 2010; Lajiness-O'Neill, et al., 2006) have also been linked to psychotic symptoms in 22qDS. Thus, the construct of social cognition does not appear to be uniquely linked to psychotic symptoms in 22qDS, but, in this sample, does appear to be more strongly linked to positive symptoms. Perhaps because social cognition requires the interaction of multiple cortico-limbic brain regions, understanding how connectivity between these brain regions is disrupted in 22qDS, and how this 'dysconnectivity' is related to behavioral dysfunction, may provide us with a better view of how social cognition and psychotic symptoms manifest in 22qDS.

In our sample, we used two measures from the SIPS to represent "psychosis risk." Similar to this approach, previous studies of youth at "clinical high-risk" or "putatively prodromal" were included as participants, based on the presence of sub-threshold psychotic symptoms (e.g, Miller, et al., 2003). In clinical high-risk samples, higher symptom severity of positive symptoms at baseline has predicted later conversion to psychosis (Cannon, et al., 2008; Schlosser, et al., 2011), suggesting that the SIPS is a valid measure of psychosis risk. Furthermore, research on the prevalence of psychotic symptoms in the general population

supports a dimensional approach (Johns & van Os, 2001). Given that 22qDS represents a genetically homogenous sample of individuals with high psychosis risk, a dimensional perspective may provide us with more traction in regards to understanding how genetic factors contribute to the etiology of psychotic symptoms, particularly in terms of understanding the relationship between phenotypes and genes. For example, it may be informative to apply novel systems biology approaches, which have been applied in other psychiatric disorders (Oldham, et al., 2008), to better understand networks of gene expression in relate to dimensional psychotic symptoms in 22qDS.

Examining predictors of psychotic symptoms in 22qDS offers an opportunity to delineate a relatively homogenous developmental pathway to psychosis. Given increasing evidence for a significant role of multiple rare mutations in the etiology of schizophrenia (Stefansson, et al., 2008), paired with the marked heterogeneity associated with the disorder (Sebat, Levy, & McCarthy, 2009), studying more homogenous, highly penetrant genetic subtypes of the illness such as 22qDS may provide traction that would otherwise be obscured when studying idiopathic schizophrenia and/or CHR youth. Moreover, overlap in neurocognitive deficits between the 22qDS subtype of schizophrenia and those with idiopathic schizophrenia (Chow et al., 2006; van Amelsvoort, et al., 2004) suggests that those with 22qDS and schizophrenia share general characteristics of cognitive expression with idiopathic schizophrenia. Recent findings also suggest that there are similar risk factors for psychosis in youth at clinical high risk (CHR) for the illness and 22qDS. In line with our findings, greater social impairment has been shown to contribute uniquely to the prediction of psychosis in CHR youth (Cannon, et al., 2008). Similarly, like those with 22qDS, a drop in verbal IQ had also been identified as a significant predictor of psychotic symptoms in CHR individuals (Seidman, et al., 2010). Identifying

converging evidence in both those at clinical and genetic high risk for psychosis is a compelling method for better understanding the behavioral and biological mechanisms underlying development of psychosis in the general population.

Several limitations of this study should be noted. First, a cross-sectional sample was used and we were not able to examine how baseline measures (or change in baseline measures) predicted psychotic symptoms over time. Second, we were not able to address causality; do social cognition impairments appear before the presence of psychotic symptoms or vice versa? However, this study sets a strong foundation for examining the role of social cognition as a predictor of psychosis in future, longitudinal studies, in both those at clinical and genetic high risk for the illness. Additionally, the majority of the 22qDS participants in our sample were not fully psychotic (6 22qDS participants had a diagnosis of a psychotic disorder), as we used dimensional measures of positive and negative symptoms as our dependent variable. Nevertheless, given the perspective that psychotic symptoms are continuously distributed in the general population (Ahmed, Buckley, & Mabe, 2011), utilizing a dimensional approach may be more powerful than looking at psychotic symptoms as a categorical variable. Finally, not all neurocognitive measures that have been identified as potential endophenotypes for psychosis, such as sustained attention (Cornblatt & Malhotra, 2001), were used in this study. Therefore, further studies comparing the predictive ability of these measures to predict psychotic symptoms in 22qDS, in comparison to social cognitive measures are warranted.

In the future, it will be important to discern whether changes in structural or functional connectivity between social-cognitive brain regions predict psychotic symptom development, particularly since previous cross-sectional studies have found relationships between psychotic symptoms and brain regions associated with social cognition in 22qDS (i.e., cingulate gyrus,

Dufour, et al., 2008). Recently, a relatively large longitudinal study found that, over time, gray matter reductions in the superior temporal gyrus (STG) were uniquely predictive of increased severity of positive psychotic-like symptoms at follow-up in 22qDS youth (Kates, Antshel, et al., 2011). These findings converge with those of Chow et al. (2011), who found that, in comparison to adults with 22qDS without schizophrenia, those with 22qDS and a diagnosis of schizophrenia displayed significant STG reductions (Chow et al., 2011). The superior temporal area has been repeatedly implicated in studies of social cognition in healthy individuals, in both tasks of ToM and emotion processing (Lieberman, 2007). Interestingly, to our knowledge, no studies have yet examined connectivity-based brain measures (i.e., diffusion tensor imaging) as significant predictors of psychosis in 22qDS. Given that white matter tracts connecting nodes of the 'social cognitive brain network' are also likely to play an important role in the development of social cognition skills, future studies are warranted to investigate whether disrupted white matter development may contribute to both social cognitive impairment and psychotic symptoms in 22qDS. Considering that both social impairment and neuroanatomic abnormalities predate the onset of psychosis (e.g., Schiffman, et al., 2004; Sun, et al., 2009), such findings will provide important information regarding which 'level of analysis' offers the most traction with regard to prediction of psychosis risk in 22qDS.

Study 1: Tables

Table 1: Demographic and Clinical Characteristics of Study Participants

	22qDS Participants (n=31)		**Healthy Comparison Participants (n=31)**		
Age (years, +/- SD)	15.9	(4.2)	15.6	(3.3)	*p*=.74
Participant Education (years,+/- SD)	8.2	(3.8)	9.2	(3.4)	*p*=.28
Parental Education (years,+/- SD)	16.3	(2.9)	16.7	(3.2)	*p*=.62
Gender (N, % female)	16	(52%)	14	(45%)	*p*=.61
Race (Asian/African American/ Caucasian/Multiple)	0/0/27/4		2/2/19/8		*p*=.08
Ethnicity (N, % Latino)	6	(19%)	8	(26%)	*p*=.54
Psychotic Disorder Diagnosis (N, %)	6	(19.4%)	NA		
SIPs Positive Symptoms (mean, +/-SD)	9.2	(7.2)	1.1	(1.6)	*p*<.001
SIPs Negative Symptoms (mean, +/-SD)	9.8	(6.9)	1.1	(1.7)	*p*<.001
SIPs Disorganized Symptoms (mean, +/SD)	5.7	(4.0)	0.6	(0.9)	*p*<.001
SIPs General Symptoms (mean, +/-SD)	5.4	(4.3)	1.0	(1.3)	*p*<.001
Psychotropic Medication (N, None/Antipsychotics/Anti-depressants)	23/4/4		NA		

Table 2: Mean raw score for non-social and social cognition measures for 22q11.2 participants and healthy controls, t-tests for equality of means, and Cohen's *d* effect sizes.

	22q11.2 Participants		**Control Participants**		***t***	***p***	***d***
	Mean	Standard Deviation	Mean	Standard Deviation			
Non-social Cognition							
Verbal Knowledge Vocabulary	37.2	(10.3)	57.8	(12.6)	6.9	$p<.001$	1.8
Visuospatial Skills Matrix Reasoning	14.6	(7.5)	26.9	(5.0)	7.6	$p<.001$	1.9
Short-Term Working Memory University of Maryland Letter Number Sequencing	8.8	(4.1)	15.6	(3.5)	6.9	$p<.001$	1.8
Processing Speed Brief Assessment of Cognition in Schizophrenia Symbol Coding	36.9	(11.4)	59.9	(15.2)	6.7	$p<.001$	1.7
Social Cognition							
Emotion Recognition Penn Emotion Recognition Task	28.7	(4.8)	32.7	(4.4)	3.4	$p=.001$	0.9
Emotion Differentiation Penn Emotion Differentiation Task	17.7	(7.0)	25.7	(6.3)	4.7	$p<.001$	1.2
Theory of Mind The Awareness of Social Inference Test	41.9	(5.0)	54.0	(5.7)	8.9	$p<.001$	2.3

Table 3: Correlation coefficients of age and non-social and social cognition measures in 22q11.2 participants and healthy controls, along with the Fisher r-to-z transformations to test for equality of correlations.

	r	*p*	*d*	*r*	*p*	*d*	*Z*	*p*
Non-social Cognition								
	22q11.2 Participants			**Control Participants**			**Fisher r-to-z test for Equality of Correlations**	
Verbal Knowledge Vocabulary	.42	.02	.93	.71	<.001	2.0	1.65	.10
Visuospatial Skills Matrix Reasoning	.09	.64	.18	.39	.03	.85	1.2	.23
Short-Term Working Memory University of Maryland Letter Number Sequencing	.29	.12	.61	.75	<.001	2.3	2.48	.01
Processing Speed Brief Assessment of Cognition in Schizophrenia Symbol Coding	.55	.002	1.3	.52	.003	1.2	.05	.99
Social Cognition								
Emotion Recognition Penn Emotion Recognition Task	.18	.35	.37	.32	.08	.68	.57	.57
Emotion Differentiation Penn Emotion Differentiation Task	.18	.35	.37	.43	.02	.95	1.05	.29
Theory of Mind The Awareness of Social Inference Test	.32	.08	.68	.55	.001	1.3	1.03	.30

Table 4: Exploratory Analyses for Social Cognition Measures in 22q11.2 Microdeletion Syndrome vs. Typically Developing Controls

Dependent Variable	**Fixed Factors**	**ANOVA Results**		
		df	***F***	***p***
Emotion Recognition	Group x Emotion	4,56	2.6	.04
Penn Emotion	Group	1,59	11.8	.001
Recognition Task	Emotion	4,56	76.1	<.001
Emotion Differentiation	Group x Emotion	1,59	3.8	.06
Penn Emotion	Group	1,59	22.4	<.001
Differentiation Task	Emotion	1,59	30.4	<.001
Theory of Mind	Group x Vignette Type	1,59	1.9	.18
The Awareness of Social	Group	1,59	78.6	<.001
Inference Test	Vignette Type	1,59	3.1	.09

Dependent Variable	**22qDS participants**		**Healthy Comparison Participants**		**Group Differences**		
	Mean	Standard Deviation	Mean	Standard Deviation	***t***	***p***	***d***
Emotion Recognition							
Anger	3.8	(1.5)	5.0	(1.4)	3.1	.003	.83
Fear	6.4	(1.5)	6.6	(1.4)	0.6	.57	.13
Happy	7.4	(0.7)	7.8	(0.5)	2.8	.007	.66
No Emotion	6.2	(2.4)	6.8	(2.1)	1.2	.25	.27
Sad	4.8	(1.9)	6.4	(1.2)	3.9	<.001	1.0
Emotion Differentiation							
Happy	7.4	(3.7)	12.2	(3.9)	4.9	<.001	1.3
Sad	10.3	(3.9)	13.5	(3.0)	3.7	.001	.92
Theory of Mind							
Lies	21.1	(3.6)	28.1	(3.2)	8.1	<.001	2.1
Sarcasm	20.8	(4.0)	25.9	(4.3)	7.0	<.001	1.3

Table 5: Predictors of Positive Symptoms in Patients with 22q11.2 Microdeletion Syndrome

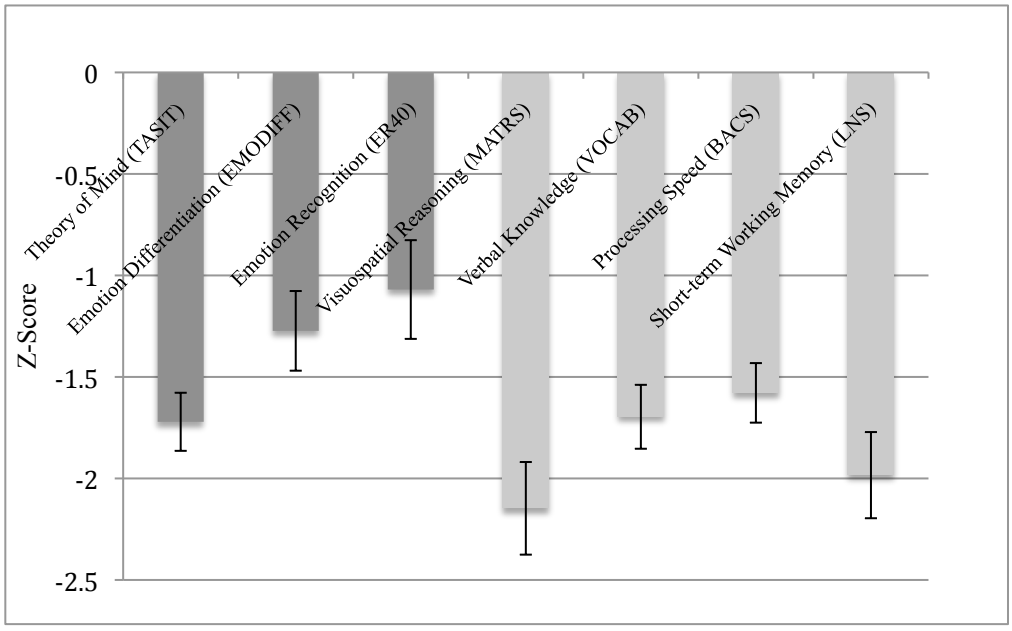
Task	*F*	*p*	R^2	Standardized b-value
Theory of Mind The Awareness of Social Inference Test	8.6	.001	39	-.66
Processing Speed Brief Assessment of Cognition in Schizophrenia Symbol Coding	4.3	.02	24	-.59
Verbal Knowledge Vocabulary	4.3	.02	24	-.54
Short-term Working Memory University of Maryland Letter Number Sequencing	3.8	.04	22	-.49
Emotion Differentiation Penn Emotion Differentiation Task	3.5	.05	21	-.46
Emotion Recognition Penn Emotion Recognition Task	2.6	.10	16	-.41
Visuospatial Skills Matrix Reasoning	2.6	.10	16	-.41

Table 6: Predictors of Negative Symptoms in Patients with 22qD11.2 Microdeletion Syndrome

Task	*F*	*p*	R^2	Standardized b-value
Processing Speed Brief Assessment of Cognition in Schizophrenia Symbol Coding	8.0	.002	37.2	-.67
Short-term Working Memory University of Maryland Letter Number Sequencing	4.9	.02	26.6	-.47
Emotion Recognition Penn Emotion Recognition Task	4.9	.02	26.5	-.46
Theory of Mind The Awareness of Social Inference Test	3.8	.04	22.0	-.42
Emotion Differentiation Penn Emotion Differentiation Task	2.7	.09	16.5	-.33
Verbal Knowledge Vocabulary	2.2	.13	14.0	-.31
Visuospatial Skills Matrix Reasoning	1.5	.24	10.2	-.20

Study 1: Figures

Figure 1: Performance across Non-social and Social Cognitive Domains in 22q11.2 Microdeletion Syndrome. Z-scores for the 22q11.2 participants were created using the mean control scores for each task. Social Cognition tasks are shown in dark grey; non-social cognition tasks are in light grey. Abbreviations for the tasks and the construct that they measure are as follows: TASIT= The Awareness of Social Inference Test, Theory of Mind; EMODIFF= Penn Emotion Differentiation Task, emotion differentiation; ER40= Penn Emotion Recognition Task, emotion identification; MATRS= Matrix Reasoning, visuospatial skills, VOCAB= Vocabulary, verbal knowledge; BACS=Brief Assessment of Cognition in Schizophrenia Symbol Coding Task, processing speed; LNS=University of Maryland Letter Number Sequencing Task, working memory.



Study 1: Supplemental Materials

Supplementary Table 1: Correlation values of Global IQ and social cognition measures in 22q11.2 participants and healthy controls.

			Emotion Recognition Penn Emotion Recognition Task	**Emotion Differentiation** Penn Emotion Differentiation Task	**Theory of Mind** The Awareness of Social Inference Test
22q11.2 Participants	IQ	*r*	.45	.22	.61
		p	.01	.25	<.001
Healthy Controls		*r*	.33	.53	.49
		p	.07	.002	.005

Supplementary Table 2: Non-social and social cognition predictors of positive symptoms in 22q11.2 Microdeletion Syndrome, participants prescribed antipsychotics removed from analyses

Task	F	p-value	R^2	Standardized b-value
Theory of Mind The Awareness of Social Inference Test	4.0	.03	25.2	-.53
Visuospatial Skills Matrix Reasoning	2.6	.09	17.9	-.39
Verbal Knowledge Vocabulary	2.5	.10	17.2	-.43
Processing Speed Brief Assessment of Cognition in Schizophrenia Symbol Coding	2.4	.11	17.1	-.49
Emotion Differentiation Penn Emotion Differentiation Task	1.2	.33	8.8	-.27
Short-term Working Memory University of Maryland Letter Number Sequencing	1.0	.38	7.7	-.26
Emotion Recognition Penn Emotion Recognition Task	.49	.62	4.0	-.14

Supplementary Table 3: Non-social and social cognition predictors of negative symptoms in 22q11.2 Microdeletion Syndrome, participants prescribed antipsychotics removed from analyses

Task	F	p-value	R^2	Standardized b-value
Processing Speed Brief Assessment of Cognition in Schizophrenia Symbol Coding	3.7	.03	23.6	-.60
Short-term Working Memory University of Maryland Letter Number Sequencing	1.7	.19	12.6	-.37
Verbal Knowledge Vocabulary	1.2	.31	9.3	-.32
Visuospatial Skills Matrix Reasoning	1.1	.35	8.4	-.27
Emotion Recognition Penn Emotion Recognition Task	.80	.46	6.2	-.24
Theory of Mind The Awareness of Social Inference Test	.65	.53	5.1	-.23
Emotion Differentiation Penn Emotion Differentiation Task	.22	.8	1.8	-.10

Are Abnormalities in Social Cognitive Neural Circuitry Related to Psychotic Symptoms in 22q11.2 Microdeletion Syndrome?

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Abstract

Introduction: 22q11.2 Deletion Syndrome (22qDS) is a neurogenetic disorder in which 30% of adolescents and young adults develop psychotic illness. Given that common biological mechanisms may underlie both social cognitive impairments and psychosis, we sought to examine: 1) alterations in brain volume, cortical thickness, and surface area in 22qDS patients, relative to typically developing controls, in neuroanatomic regions associated with social cognition; 2) whether there was an altered age-related trajectory of these brain regions in 22qDS; and 3) whether neuroanatomic alterations in these brain regions were significantly associated with psychotic symptoms and social cognition in 22qDS patients.

Methods: High-resolution T1-weighted scans were collected on 65 participants (31 22qDS, 34 controls, age range: 10-25 years old) and all image processing was conducted through the FreeSurfer image analysis suite. Measures of volume, cortical thickness, and surface area were extracted from the following "social cognitive" brain regions of interest: amygdala, fusiform gyrus, superior temporal gyrus, insula, anterior cingulate, superior frontal cortex, middle frontal cortex, and inferior frontal cortex. The occipital cortex was also investigated as a control region. Social cognition domains assessed were: emotion recognition, emotion differentiation, and Theory of Mind (ToM). Positive symptoms were assessed using the Structured Interview for Prodromal Symptoms (SIPS).

Results: In comparison to typically developing controls, 22qDS participants showed disruptions in multiple brain regions associated with social cognition. In particular, those with 22qDS had increased cortical volumes in bilateral orbitofrontal cortices and insula, which appeared to be driven by increased cortical thickness in these regions. Exploratory analyses revealed that the increased cortical thickness in the right medial orbitofrontal cortex was significantly associated

with increased positive symptom severity in 22qDS (r=.46, p=.009). Increased right amygdala volume was associated with better ToM performance in 22qDS (r=.38, p=.03). A pattern of age-associated cortical thinning was observed in control subjects in the left fusiform gyrus and right occipital cortex; however, this relationship was disrupted in 22qDS participants. When testing the joint contribution of behavioral and neuroanatomic measures to prediction of positive symptoms in 22qDS, we found that cortical thickness in the right medial orbitofrontal cortex and ToM task performance accounted for 43% of the variance in positive symptoms in 22qDS. Conclusion: These findings provide preliminary evidence that neuroanatomic regions relevant to social cognition may be useful endophenotypes to pursue with regard to psychosis risk in 22qDS.

Introduction

Social dysfunction is considered to be a hallmark feature of schizophrenia. These patterns of social dysfunction are likely consequences of deficits in social cognition (Couture, et al., 2006), the ability to understand the intentions of others and act accordingly (Adolphs, 2001). Key neural circuits believed to be involved in social cognition are consistent with neural deficits found in people with schizophrenia (Pinkham, Penn, Perkins, & Lieberman, 2003). Therefore, these findings suggest that common biological mechanisms may underlie social cognitive impairments and psychosis. At the same time, newly emerging evidence suggests that rare genetic mutations that disrupt neurodevelopment may play a larger role in psychotic illness than was previously believed. Individuals with a specific genetic syndrome known as 22q11.2 microdeletion syndrome (22qDS) have shown increased rates of conversion to schizophrenia, as high as 30% (Gothelf, Feinstein, et al., 2007). Investigation of social cognitive deficits in the context of this highly penetrant genetic mutation provides a unique opportunity to identify intermediate traits associated with genetic mechanisms involved in schizophrenia risk. Like those with idiopathic schizophrenia, individuals with 22qDS have difficulty initiating and maintaining friendships, display lack of skill in social situations, and show increased levels of social withdrawal (Baker & Skuse, 2005; Swillen, et al., 1997). However, the neurobiological substrates of social cognitive deficits, and their relationship to psychosis, have not been investigated in 22qDS.

Though a large network of brain regions is likely involved in processing social information, several specific brain areas are consistently associated with social cognitive task performance (Blakemore, 2008a; Lieberman, 2007). In particular, the amygdala and lateral fusiform gyrus are believed to be involved in emotion processing, or the capacity to identify or

discriminate between different emotions (Adolphs, Tranel, Damasio, & Damasio, 1994; Hornak, Rolls, & Wade, 1996). Evidence from lesion studies and functional magnetic resonance imaging (fMRI) studies implicates the ventro- and dorsomedial prefrontal cortex and anterior cingulate cortex in ToM abilities (Frith & Frith, 1999; Brunet, Sarfati, Hardy-Bayle, & Decety, 2000; U. Frith & Frith, 2003; Rudebeck, Bannerman, & Rushworth, 2008; Sebastian, et al., 2012; Shamay-Tsoory & Aharon-Peretz, 2007). Finally, the superior temporal sulcus (STS), orbitofrontal cortices, and insula are believed to play a role in both emotion processing and ToM (Brunet-Gouet & Decety, 2006; Carrington & Bailey, 2009; Wicker, et al., 2003). Animal models also support the role of these brain region in social cognition; for example, neuronal activity recorded in the dorsal anterior cingulate and amygdala of monkeys was temporally associated with time spent viewing another monkey (Livneh, Resnik, Shohat, & Paz, 2012), while larger STS gray matter volume significantly correlates with larger social networks in macaques (Sallet, et al., 2011).

During adolescence, rapid changes take place in both the social realm and brain maturation (Blakemore, 2008a). Notably, adolescence is also the peak period of onset for schizophrenia (Paus, Keshavan, & Giedd, 2008). Brain maturational changes during this time period are likely to map onto behaviors that also undergo rapid developmental shifts during adolescence, such as social cognition (Blakemore, 2008b). For example, two studies have shown that when observing neural responses to a social cognition task, in comparison to adults, healthy adolescents showed significantly more activation in the medial prefrontal cortex, which the authors interpret as a developmental shift in activation from anterior to more posterior brain regions (Blakemore, den Ouden, Choudhury, & Frith, 2007; Burnett, et al., 2009). One hypothesis for the increased involvement of the medial prefrontal cortex in adolescents is that

they are still developing social skills necessary to appropriately interact in interpersonal situations, and require increased activation of frontal regions relative to adults (Burnett & Blakemore, 2009). These developing social skills, which are presumably supported by distinct neural networks, have yet to become "automatic" for adolescents, as the efficiency and connectivity of the relevant brain areas are still being refined with the acquisition of new social experiences. Therefore, examining age-associated changes in social cognitive neural circuitry in adolescents and young adults with 22qDS may help elucidate the role of aberrant brain maturational processes in social cognitive development and in the development of psychotic symptoms.

Current research on structural neuroanatomy in 22qDS suggests that this population has neuroanatomic abnormalities in regions associated with social cognition, and some of these areas have been linked to psychotic symptoms in 22qDS. Two previous studies have identified increased insula volumes in children with 22qDS (Campbell et al., 2006; Kates, Bansal, et al., 2011). A volumetric study of 22qDS youth found reductions in the bilateral cingulate gyrus (driven by the anterior cingulate gyrus), and right cingulate gyrus volume was associated with psychotic symptoms (Dufour, et al., 2008). Though a small longitudinal study of 22qDS adolescents and young adults did not detect significant volumetric differences between participants who developed psychosis over the follow-up period and those that did not, 22qDS individuals overall had significantly greater decreases in amygdala volume over time, relative to typically developing controls, along with a differential increase in superior temporal gyrus (STG) volumes (Gothelf et al., 2007). Kates and colleagues (2011) showed that, over an average of a 3.2-year follow-up period, decreases in STG volume predicted positive psychotic symptoms – as assessed by the SIPS – at follow-up in adolescents with 22qDS. Cross-sectional findings from

Bearden et al. (2004) complement this study, as reduced temporal gray matter was associated with severity of Thought Problems in non-psychotic youth with 22qDS. Finally, using a novel structural MRI technique, Bearden et al. (2009) found highly significant cortical thinning in the anterior cingulate cortex, medial frontal gyrus, and subgenual prefrontal cortex in 22qDS individuals - brain regions critical for emotion regulation. Thus, disruptions in brain areas associated with social cognition have been observed in 22qDS, and may also underlie psychotic symptoms in this syndrome.

In all currently published structural magnetic resonance imaging studies in 22qDS, only one neuroanatomic measure (i.e., volume or cortical thickness) has been used to examine group differences, or relationships with behavioral measures. However, it may be more informative to look at multiple neuroanatomic measures (e.g., volume, cortical thickness, and surface area), due to findings suggesting that these indices are driven by different genetic and neurobiological mechanisms (Winkler, et al., 2010). Furthermore, considering that volume measures are derived from indices of both cortical thickness and surface area, disruptions in these two measures may cancel each other out and the volume may appear "normal", obscuring important underlying neuroanatomic differences. Therefore, in this study we assessed measures of volume, cortical thickness and surface area for all neuroanatomic regions investigated.

The first goal of this study was to examine structural alteration of brain regions associated with social cognition in 22qDS as compared to demographically comparable controls. Based on previous findings, we hypothesized that those with 22qDS would have increased volume in the insula and orbitofrontal cortices (Campbell et al., 2006; Kates, Bansal, et al., 2011) and decreased anterior cingulate volumes (Dufour, et al., 2008), particularly given the evidence that the midline structures of the brain are differentially affected in 22qDS (e.g., Bearden, et al.,

2009). The second goal of this study was to examine whether the developmental trajectory of these social brain areas in 22qDS differs from healthy controls. We hypothesized that the typical adolescent developmental trajectory (i.e., cortical thinning with increasing age, Fjell, et al., 2009; Tamnes, et al., 2010) would be disrupted in those with 22qDS. The third goal of this study was to determine whether "social cognitive" brain regions/networks account for variability in positive symptoms and/or social cognition performance in 22qDS patients. Based on the framework that social cognitive brain regions overlap with brain areas most often affected in schizophrenia (Pinkham, et al., 2003), we hypothesized that these same regions will be relevant to the development of positive symptoms in 22qDS patients, particularly the superior temporal gyrus and anterior cingulate. Finally, as an exploratory analysis, we jointly examined the contribution of neuroanatomic measures and behavioral tasks of social cognition to the prediction of positive symptoms in 22qDS, to determine whether these neuroanatomic markers show unique predictive power over and above that of behavioral measures.

Methods

Participants

The total sample consisted of 65 participants (10-25 years old, 31 22qDS and 34 controls). 22qDS participants consisted of individuals with a molecularly confirmed diagnosis of 22q11.2 deletion syndrome recruited from an ongoing longitudinal study at the University of California, Los Angeles (UCLA). Healthy controls were also recruited from this study. Exclusion criteria for all study participants were: neurological or medical condition disorder that might affect performance, insufficient fluency in English, and/or if they endorsed substance or alcohol abuse and/or dependence within the past six months. Controls additionally must not meet criteria for any major mental disorder, with the exception of attention deficit-hyperactivity

disorder (ADHD) or past episode of depression, based on information gathered during administration of the Structured Clinical Interview for DSM-IV Axis I Disorders (First, Spitzer, Gibbon, & Williams, 1997).

All participants underwent a verbal and written informed consent process. Participants under the age of 18 years provided written assent, while their parent or guardian completed written consent. The UCLA Institutional Review Board (IRB) approved all study procedures and informed consent documents.

Measures

Structured Interview for Prodromal Syndromes

A master's level trained clinician assessed all participants on the positive, negative, disorganized, and general symptom scales from the Structured Interview for Prodromal Syndromes (SIPS; McGlashan, 2001). Symptoms on these scales are rated from 0-6, with zero representing an absence of symptoms and six referring to an extremely severe level of symptoms. This measure has shown excellent inter-rater reliability (above .75, Meyer, et al., 2005; Miller, et al., 2003). All raters demonstrated good inter-reliability for symptom ratings, with kappa values ranging from 0.85 to 1.00. For the purposes of this study, we used the sum of the SIPS positive symptom scores as a dimensional measure of psychotic symptoms. This measure encompasses a range of symptom severity, including sub-threshold (prodromal) and fully psychotic symptoms.

Social Cognition Tasks

Study participants received the Penn Emotion Recognition Test (ER40), a computerized emotion identification task in which 40 color photographs of adult faces, varying in race and gender, are presented randomly (Kohler, et al., 2000). Participants were asked to identify the

emotion of each face (happy, sad, anger, fear, or no emotion) and were given as long as needed to respond (total maximum score = 40, with each emotion presented 8 times). Participants also received the Penn Emotion Differentiation Task (EMODIFF), a computerized emotion differentiation task in which individuals are presented with two black and white images of faces of the same person and are asked to choose which of the two faces displayed expresses an emotion more intensely (e.g., more happy, more sad), or decide that the two faces are equally happy or sad (total maximum score = 40) (Erwin, et al., 1992). Both measures have shown adequate construct validity and test-retest reliability (Carter, et al., 2009; Rojahn, et al., 2000), have been widely used in studies with schizophrenia patients (e.g., Butler, et al., 2009; Sachs, et al., 2004; Silver, et al., 2002), as well as in adolescents (Roddy, et al., 2012; Schenkel, et al., 2007).

All participants were administered Part 3 of The Awareness of Social Inference Test (TASIT, McDonald, et al., 2003). The TASIT is a computerized task believed to assess one's ability to comprehend the intentions of others, particularly how one comprehends white lies or sarcasm. The task consists of 16 vignettes (each lasting between 15-60 seconds), eight of which show an individual telling a lie, while the other eight display an interaction in which someone uses sarcasm. After viewing each vignette, an assessor asked the participant four questions related to the scene: 1) what someone is doing to another person in the scene, 2) what someone is trying to say to the other person, 3) what one of the individuals in the scene is thinking, and 4) what one of the characters in the vignette is feeling. After task completion, an overall score was calculated (maximum = 64). The TASIT has shown adequate reliability and validity with brain-injured patients (McDonald, et al., 2006), and has been used with adolescents at clinical high-risk

for psychosis, along with first-episode and chronic patients with schizophrenia (M. F. Green, et al., 2011).

Image Acquisition

All scanning was carried out on a Siemens 3 Tesla "Tim Trio" MRI scanner at the Brain Mapping Center at UCLA (22qDS=17, controls=17) or at the Center for Cognitive Neuroscience (22qDS=14, controls=17). Measures of brain structure were obtained with high-resolution structural MRI. Each scan began with a 10-minute acquisition of standard images used for determining regional anatomy, including a sagittal localizer image (TR/TE=500/10ms, 192x256 matrix), a high-resolution T2-weighted axial image (TR/TE=5000/33 ms, 128x128 matrix, FOV=200x200mm), and a sagittal 1 cubic mm T1-weighted image (MPRAGE, TR/TE = 2300/2.91, flip angle = 9 degrees; slice thickness = 1.20 mm, 240x256 acquisition matrix).

Structural MRI analysis

The FreeSurfer image analysis suite (version 5.0, http://surfer.nmr.mgh.harvard.edu) surface-based processing pipeline was used to derive measures of volume, cortical thickness, and surface area. Freesurfer is a well-validated processing protocol that has been previously described in detail (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). In short, the following steps were taken in the processing stream: motion correction, transformation of images to standard Talairach space, intensity normalization, removal of non-brain tissue, segmentation of white matter and subcortical structures, and final segmentation of cortical surfaces. Final segmentation is based on both a subject-independent probabilistic atlas and subject-specific measured values. Raters (MJ, AP, RJ) blind to diagnosis visually inspected the scans at several points along the processing pipeline and manually edited any errors. Using an automated computer algorithm, cortical thickness estimates were derived by taking the distance between the

gray–white matter border and the pial surface at each vertex (Fischl & Dale, 2000) . Surface area was calculated by taking the sum of the area of the vertices in each parcellation. Volume was then calculated as the product of the surface area and cortical thickness for each region. The following structures, which include both areas hypothesized to be related to social cognition and a control region (occipital cortex), were examined: amygdala, fusiform gyrus, superior frontal cortex, superior temporal gyrus, insula, anterior cingulate, middle frontal cortex, inferior frontal cortex, and occipital cortex (Figure 1).

Statistical Analyses

Statistical analyses were performed using SPSS software v. 21 (Chicago, Illinois) and SAS/STAT software (SAS Institute Inc., Cary, NC, USA). We compared demographic characteristics between groups using independent samples t-tests for continuous variables and chi square test for categorical variables. To ensure that there were no cross-scanner differences, for all neuroanatomic measurements, we conducted a univariate analysis of covariance (ANCOVA) for each identified region in each hemisphere, with scanner type as the between-groups factor and group as a covariate.

All neuroanatomic measures were examined for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests and transformed appropriately if they violated the assumptions of normality. To compare sMRI brain volume and surface area in 22qDS vs. controls, we conducted an ANCOVA for each identified region in each hemisphere, with diagnosis (22qDS vs. control) as the between subjects factor and total intracranial brain volume, sex, and age as the covariates. For cortical thickness, an ANCOVA was also conducted for each identified region, with age and sex as covariates. Due to the large number of comparisons (56 total), False Discovery Rate (FDR) q-values were estimated using SAS/STAT software (SAS Institute Inc.,

Cary, NC, USA). To determine that outliers were not driving any of our significant differences, these analyses were also re-run with outliers (those with values > 3 standard deviations away from the mean neuroanatomic measure) removed.

To address whether the relationship between age and neuroanatomic measurements differed between groups, we first examined visually the scatter plots of age vs. all neuroanatomic measures. In plots that visually appeared to have promising age*group interactions, we then added age*group interaction terms to the original ANCOVA models for each brain region. This resulted in a total of 5 analyses: cortical thickness in left middle frontal cortex, and bilateral regions of the fusiform gyrus and occipital cortex.

For statistical analyses corresponding to the third aim of our study (i.e., to determine whether the brain regions investigated above account for variability in positive symptoms and social cognition in 22qDS patients), residuals were first calculated from each variable, after regressing out the effects of age and sex. Then, Pearson correlations (corresponding to partial correlations) were conducted between each neuroanatomic brain region with residualized positive symptoms and social cognition variables. For this exploratory analysis we did not adjust for multiple comparisons, in order to generate hypotheses for future, larger studies.

Finally, to explore the ability of combined behavioral and neuroanatomic measures to predict variance in positive symptoms in 22qDS, we conducted a linear regression analysis and entered the most significant behavioral predictor we previously identified (TASIT), (Jalbrzikowski, et al., 2012), along with age, sex, and any neuroanatomic measure(s) that showed a significant association with 22qDS as predictors, and positive symptoms as the dependent variable. We also ran another separate, linear regression analysis with TASIT, age, and sex as predictors and positive symptoms as the dependent variable. To compare whether the combined

model improved the amount of variance accounted for in positive symptoms in 22qDS, we conducted an R-squared change test between the two models.

Results

As shown in Table 1, 22qDS patient and control groups were matched on all demographic factors (all p-values ≥ 0.13). As expected, there were no scanner differences in volume (all p-values ≥ 0.10), cortical thickness (all p-values ≥ 0.26), or surface area (all p-values ≥ 0.09; see Supplemental Materials, Table 1).

Volumetric Results

Results of group comparisons for brain volumes are presented in Table 2. After correcting for multiple comparisons, individuals with 22qDS had significantly smaller volumes than controls in the following bilateral regions: fusiform gyrus, anterior cingulate gyrus, and occipital cortex. 22qDS participants also had significantly reduced brain volumes in the right superior temporal and right middle frontal regions, as well as the left amygdala. In contrast, in bilateral regions of the insula and orbitofrontal cortex, individuals with 22qDS had greater volumes than controls. However, there were no significant differences between groups in superior frontal and inferior frontal cortices. When these analyses were repeated without the outliers included, all of the above results remained significant and no other results reached significant.

Surface Area Results

Results for the group comparisons of brain surface area are also presented in Table 2. In comparison to controls, 22qDS participants had reduced surface area in bilateral regions of the fusiform, anterior cingulate, middle frontal, and occipital cortex. 22qDS participants also showed decreased surface area in the right superior temporal region in comparison to controls.

Similar to the volumetric results, there were no significant differences between 22qDS participants and controls in surface area measurements of the superior and inferior frontal regions. Additionally, there were no differences between 22qDS participants and controls in surface area measurements of the orbitofrontal cortices and the insula. When these analyses were repeated without the outliers included, all of the above results remained significant and no other results reached significance.

Cortical Thickness Results

A different pattern of results emerged when examining group differences in cortical thickness (results are also presented in Table 2). In comparison to controls, individuals with 22qDS had *increased* cortical thickness in bilateral regions of the insula, middle frontal, inferior frontal, and orbitofrontal cortices. Increased cortical thickness was also seen in the left occipital cortex and the right fusiform area in 22qDS participants, when compared to controls. When these analyses were repeated without the outliers included, all of the above results remained significant and no other results reached significance.

*Age*Group Interactions*

Several significant results emerged when the Age*Group interaction terms were added to the ANCOVAs for each measurement. Specifically, there was a significant age*group interaction for cortical thickness in the left fusiform cortex ($F(1,60)=5.9$, $p=0.02$, eta=0.09, Figure 2A). Controls showed a pattern of decreasing cortical thickness in the fusiform with increasing age ($r=-0.49$, $p=0.003$). However, in 22qDS participants, there was no association between age and cortical thickness in this region ($r=0.05$, $p=0.79$). A similar pattern of results, indicating a significant age*group interaction, also emerged in the right occipital cortex ($F(1,60)=8.6$, $p=0.005$, eta=0.13, Figure 2B). While cortical thickness decreased with increasing

age in controls (r= -0.66, p<0.001) in this region, 22qDS participants did not show a significant relationship between age and cortical thickness in this region (r= -0.16, p=0.39).

Relationships of Brain Volumes With Social Cognition Measures in 22q11.2 Deletion Syndrome

There were no significant relationships found between social cognition performance and measures of cortical thickness or surface area in 22qDS. However, relationships between volumetric measures and social cognition tasks (ER40, EMODIFF, TASIT) in 22qDS patients indicated a consistent pattern of results. Specifically, increases in right amygdala volume were associated with better TASIT performance (r=0.38, p=0.03, Figure 3A). Additionally, relationships between ER40 performance and right amygdala volume (r=0.33, p=0.07, Figure 3B) and EMODIFF performance and right amygdala volume (r=0.35, p=0.05, Figure 3C) approached significance. Thus, better performance on both of these emotion-processing tasks was related (at trend-level) to increased right amygdala volume (Figure 3).

Relationship between Cortical Thickness and Positive Symptoms in 22q11.2 Deletion Syndrome

There were no significant relationships found between positive symptoms and measures of volume and surface area in 22qDS. However, there was a significant inverse correlation between right orbitofrontal cortical thickness and positive symptoms in 22qDS (r=-0.40, p=0.02). Increased cortical thickness in the right orbitofrontal cortex was associated with increased positive symptoms in 22qDS. We then followed up on this correlation by investigating lateral and medial orbitofrontal regions separately, as these regions are anatomically and functionally distinct (Price, 2007) (Noonan, et al., 2010). We found that this relationship was driven by variability in cortical thickness in the right medial orbitofrontal cortex (r=0.46, p=0.009), with increased cortical thickness in this region associated with more severe positive

symptoms (Figure 4A). Similarly, the relationship between the left medial orbitofrontal cortex thickness and positive symptoms approached significance (r=0.31, p=0.07, Figure 4B).

Combined Behavioral and Neuroanatomic Predictors of Positive Symptoms in 22q11.2 Deletion Syndrome

When testing the joint contribution of behavioral and neuroanatomic measures to prediction of positive symptoms in 22qDS, the overall model including both the TASIT and right medial orbitofrontal thickness as predictors of positive symptoms in 22qDS was significant ($F(4,26)=4.97$, p=0.004), with these two predictors (and covariates of age and sex) accounting for 43% of the variance in positive symptoms in 22qDS. Within this model, both the TASIT (t=-2.96, p=0.007, b=-0.49) and cortical thickness in the right medial orbitofrontal cortex (t=2.15, p=0.04, b=0.43) were significant predictors of positive symptoms. In a separate model, we then entered only the raw TASIT score (total number correct), along with age and sex as covariates, as the only predictor of positive symptoms. This overall model was significant ($F(3,27)=4.49$, p=0.01), accounting for 33% of the variance in positive symptoms. An R-squared change test between the two models showed that addition of right cortical thickness in medial orbitofrontal cortex significantly improved the ability to predict positive symptoms in 22qDS (R-squared change: 10%, p=0.04). These findings suggest that right medial orbitofrontal thickness adds unique variance to the ability of ToM performance to predict positive symptoms in 22qDS.

Discussion

To our knowledge, this is the first study to examine regional differences in socially relevant brain structures on the basis of their separable components (volume, cortical thickness, and surface area) in 22q11.2 microdeletion syndrome, a recurrent genetic mutation associated with substantial social impairment and high rates of psychosis. This study also explored

relationships between these brain regions and social cognition performance on laboratory tasks and clinician-rated positive symptoms in youth with 22qDS. These analyses yielded several novel findings: 1) based on measures of volume, cortical thickness, and surface area, multiple brain regions associated with social cognition, including the insula, orbitofrontal cortices, anterior cingulate, and fusiform gyrus, were disrupted in 22qDS; 2) exploratory analyses revealed that increased right amygdala volumes were associated with better performance on social cognition tasks, whereas increased cortical thickness in the right medial orbitofrontal cortex was associated with greater severity of positive symptoms in 22qDS; 3) the right fusiform gyrus and right occipital cortex showed cortical thinning with increasing age in typically developing controls, but this pattern of age-associated cortical thinning was not present in 22qDS; and 4) analysis of combined neuroanatomic and behavioral predictors (i.e., right medial orbitofrontal cortical thickness and ToM performance) significantly improves the ability to predict positive symptoms in 22qDS, relative to behavioral measures of social cognition.

Analysis of multiple neuroanatomic indices (e.g., volume, cortical thickness, and surface area) revealed a complex and intriguing pattern of results, which complement and extend upon previous structural MRI studies of participants with 22qDS. First, we found that multiple regions showed decreased volume in 22qDS relative to controls, including some that are critically involved in social cognition (bilateral regions of the fusiform gyrus, anterior cingulate), as well as basic visual processing regions (occipital cortices). For all of these measures, volumetric reductions were driven by significantly decreased surface area in 22qDS. Though previous studies have found volumetric reductions in occipital cortices (Campbell et al., 2006), fusiform (Shashi, et al., 2010) and cingulate areas (Dufour, et al., 2008; Shashi, et al., 2010) in 22qDS, this is the first study to show that these reductions are driven by decreased surface area.

We also found that, in comparison to typically developing controls, 22qDS individuals had increased bilateral orbitofrontal and insula volumes, replicating findings from two separate laboratories (Campbell et al., 2006; Kates, Bansal, et al., 2011). Here, we extend upon these findings by showing that increased volumes in these regions are driven by increased cortical thickness, not changes in surface area. We also found that 22qDS participants showed, in comparison to typically developing controls, reduced right amygdala volume. Additionally, adolescents and young adults with 22qDS showed increased cortical thickness in multiple neuroanatomic regions, including the right fusiform area, occipital regions, and superior and middle and interior frontal regions. Our results replicate previous findings using a different methodology in youth ages 9-15 years old, which also found multiple areas of increased cortical thickness in 22qDS relative to healthy controls, primarily in frontal brain regions (Schaer, et al., 2009).

To our knowledge, this is the first study to investigate multiple measures of structural neuroanatomy in 22qDS. Recent publications have highlighted that disruption in cortical volume may be driven by changes in surface area, cortical thickness, or a combination of both (Ecker, et al., 2013; Rimol, et al., 2012). Thus, it is critical to parse out the components driving these group differences, to help better understand the etiology of psychiatric disorders. In particular, surface area and cortical thickness have separate genetic origins (Winkler, et al., 2010), developing from different progenitors (Pontious, Kowalczyk, Englund, & Hevner, 2008). Surface area is considered to represent the number of cortical columns, while cortical thickness is a proxy for the number of cells in a column (Rimol, et al., 2012). Thus, the differential patterns of brain disruption that we see in this study (e.g., increased cortical thickness in the orbitofrontal cortices and insula, but decreased surface area in the anterior cingulate, fusiform

gyrus, and occipital cortices) suggest that these alterations may reflect disruptions at different stages of corticogenesis.

Importantly, we found that the increased cortical thickness in the right medial orbitofrontal cortex was significantly associated with more severe positive symptoms in 22qDS. Interestingly, we did not find relationships between positive symptoms and brain regions that have been previously associated with prodromal or psychotic symptoms in 22qDS, specifically the superior temporal gyrus (Kates, Antshel, et al., 2011) and anterior cingulate (Dufour, et al., 2008). The difference in results across studies may be due to a number of factors: differences in age ranges studied at baseline (Kates et al., 2011: 9-15 years old, Dufour et al., 2008: 6-37 years old), variable methods used for neuroimaging analyses, as well as differences in measures used to assess psychotic symptoms. Additionally, one of the studies investigated within-subject change over time, rather than cross-sectional associations (Kates, Antshel, et al., 2011). Though increased orbitofrontal thickness is not typically reported in individuals with idiopathic schizophrenia, there is substantial heterogeneity in volumetric findings, with some studies finding increased orbitofrontal cortical volume in first-episode schizophrenia (Szeszko, et al., 1999), while others have found reduced volumes (Convit, et al., 2001) (Gur, et al., 2000); and still other studies have failed to find significant differences between schizophrenia patients and healthy controls (Sapara, et al., 2007). These disparate findings may be due to the heterogeneous nature of schizophrenia, thus highlighting the value of investigating well characterized, homogenous subtypes of schizophrenia. Furthermore, our findings provide preliminary evidence that neuroanatomic measures associated with social cognition (i.e., right medial orbitofrontal cortical thickness), combined with behavioral measures of social cognition, may improve the prediction of positive symptoms, over and above behavioral measures of social cognition alone.

Taken together, our findings suggest that neuroanatomic measures associated with social cognition may be useful candidate endophenotypes to pursue for identification of psychosis risk in 22qDS.

Additionally, within 22qDS patients, increased right amygdala volumes were significantly related to improved social cognition performance. This finding is supported by previous fMRI which indicate a critical role of amygdala in social processing, in both healthy adults (Sergerie, Chochol, & Armony, 2008) and those with idiopathic schizophrenia (Li, Chan, McAlonan, & Gong, 2010). Though in our study reduced amygdala volumes were not related to positive symptoms, a previous study conducted by our laboratory showed that the TASIT, the social cognition task that significantly correlated with amygdala volume in this study, was the best predictor of positive symptoms in 22qDS (Jalbrzikowski, et al., 2012), when compared to other measures of social and non-social cognition. One hypothesis could be that these intermediate phenotypes, such as social cognition, are "closer" to the neural substrates associated with psychosis-proneness and are more likely to show relationships with neuroanatomic structures than are psychotic symptoms. Alternatively, reduced amygdala volumes could be associated with social cognition performance, but not related to psychosis risk.

We also found evidence of significant group*age interactions in multiple brain regions, suggesting a disrupted developmental trajectory of brain maturation of 22qDS youth. In particular, the left fusiform gyrus and right occipital cortex showed cortical thinning with increasing age in typically developing controls, as has been found in previous studies of typically developing adolescents and young adults (Tamnes, et al., 2010), but this pattern was not observed in 22qDS individuals. These findings suggest that in particular, adolescent cortical maturation development in cortical thickness of the fusiform and occipital regions may be

disrupted in 22qDS. These findings, however, need to be confirmed with longitudinal follow-up studies.

There are several limitations to this study, which should be noted. First, given the cross-sectional design we were unable to investigate baseline neuroanatomic measures, or change in these variables over time, as predictors of *subsequent* psychotic symptom development. Considering that recent findings suggest that regional neuroanatomic changes over time predict positive prodromal symptoms, assessed by the SIPS (Kates, Antshel, et al., 2011), it is critical that future studies incorporate a longitudinal approach. Additionally, it will be important to investigate whether our cross-sectional finding suggesting a disrupted trajectory of cortical thickness in the fusiform and occipital regions in 22qDS is replicated in a within-subjects, longitudinal design. Also, regarding the association of our neuroanatomic measures with positive symptoms, the majority of the 22qDS participants in our sample were not fully psychotic; only 3 22qDS participants had a diagnosis of a psychotic disorder, and thus we used dimensional measures of positive symptoms as our dependent variable. Nevertheless, given the perspective that psychotic symptoms are continuously distributed in the general population (Ahmed, et al., 2011), utilizing a dimensional approach may be more powerful than investigating psychotic symptoms as a categorical variable. Furthermore, it should be noted that individuals with 22qDS not only exhibit psychotic symptoms, but have increased risk for a number of psychiatric disorders (T. Green, et al., 2009), including autism spectrum disorders (Vorstman, et al., 2006). Therefore, it may be that several of the observed brain changes in social cognitive structures may be also associated with the development of other psychiatric disorders in 22qDS, particularly since increased cortical thickness has been found in adults with idiopathic autism spectrum disorders (Ecker, et al., 2013). Finally, our investigations of the relationships between

neuroimaging variables and behavioral measures (i.e., social cognition task performance and positive symptoms) were exploratory, and thus did not correct for multiple comparisons. Given that relationships with social cognition measures had never before been investigated, to our knowledge, and given our relatively modest sample size we chose to be less stringent and leave open the possibility for a Type I error, rather than neglect to report upon a potentially relevant finding. Indeed, our findings that multiple social cognitive measures are nominally associated with amygdala volumes suggest that this may be an important finding to follow up in larger-scale future studies.

Given that 22qDS is one of the strongest predictors of psychosis, it is important to examine how these results relate to the existing literature on idiopathic schizophrenia. At first glance, the results may seem counter-intuitive, given that many of our results were driven by increased cortical thickness, while exaggerated changes in cortical thinning in multiple brain regions has been associated with conversion to psychosis (Sun, et al., 2009; Takahashi, et al., 2009), along with poorer neuropsychological functioning and more severe clinical symptomatology in schizophrenia (Cobia, Smith, Wang, & Csernansky, 2012). However, though the direction of the effect that we found in our 22qDS may not have been predicted based on existing schizophrenia/psychosis literature, many of the regions in which we found significant differences between 22qDS participants and controls correspond to regions that show dysfunction in schizophrenia (e.g., Bora, et al., 2011; Shepherd, Laurens, Matheson, Carr, & Green, 2012). Thus, it may be that there are multiple pathways of disruption in particular brain regions relevant for the development of psychosis, resulting in similar downstream phenotypic effects. While many researchers speculate that increased cortical thinning in idiopathic schizophrenia is suggestive of an overly aggressive synaptic pruning process (Hoffman & McGlashan, 1997;

Keshavan, Anderson, & Pettegrew, 1994), it is possible that the increased cortical thickness observed in primarily frontal regions in 22qDS may be due to neuronal over-proliferation in these brain regions, resulting in a similar behavioral phenotype (e.g., positive symptoms).

Interestingly, to our knowledge, no studies have yet examined connectivity-based brain measures (i.e., diffusion tensor imaging) as significant predictors of psychosis in 22qDS. Given that white matter tracts connecting nodes of the 'social cognitive brain network' are also likely to play an important role in the development of social cognition skills, future studies are warranted to investigate whether disrupted white matter development may contribute to both social cognitive impairment and psychosis in 22qDS. Finally, given the complex relationship between genes, neuroanatomic measures, behavior, and clinical symptomatology in psychiatric disorders, it will be useful to implement systems biology based approaches in order to identify networks of co-expressed genes in relation to phenotypic data (Zhang & Horvath, 2005), particularly in populations with a well-defined genetic etiology, such as 22qDS.

Considering that both social impairment and neuroanatomic abnormalities predate the onset of psychosis (e.g., Schiffman, et al., 2004; Sun et al., 2009), these findings provide important information regarding which 'level of analysis' offers the most traction with regard to prediction of psychosis risk in 22qDS. Findings from the current study provide preliminary evidence that cortical thickness in neuroanatomic regions associated with social cognition, particularly the medial orbitofrontal cortex, may be useful endophenotypes to pursue in regards to identifying psychosis risk, both in the context of 22q11.2 microdeletion syndrome and the general population.

Study 2: Tables

Table 1: Demographic and Clinical Characteristics of Study Participants

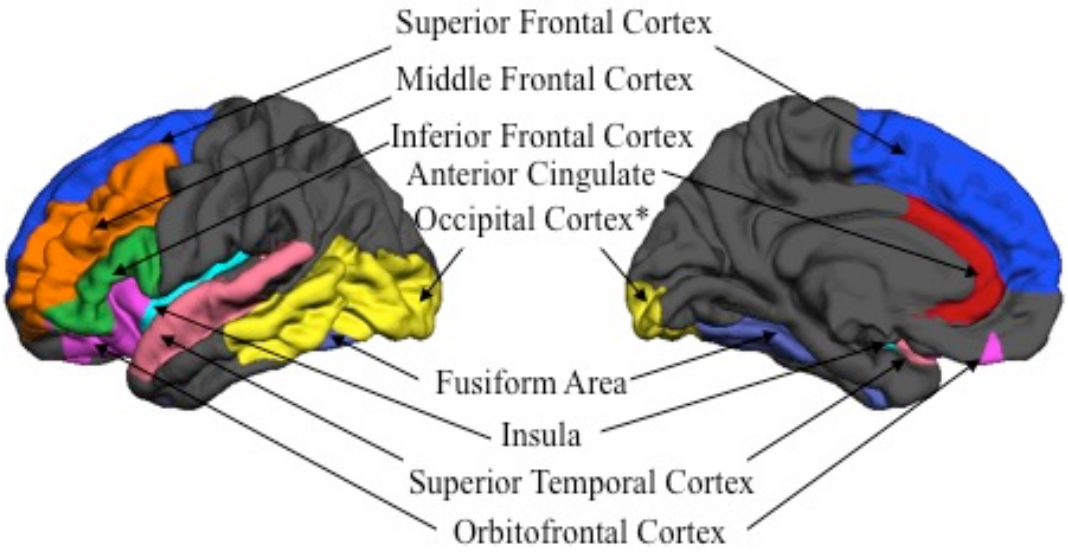
	22qDS Participants (n=31)		**Healthy Comparison Participants (n=34)**		
Age (years, +/- SD)	16.4	(4.2)	15.7	(3.8)	*p*=.47
Participant Education (years,+/- SD)	8.5	(3.7)	9.2	(3.6)	*p*=.49
Parental Education (years,+/- SD)	16.2	(2.9)	15.4	(2.9)	*p*=.27
Gender (N, % female)	16	(52%)	14	(42%)	*p*=.39
Race (Asian/African American/ Caucasian/Multiple)	0/1/27/3		3/4/22/5		*p*=.13
Ethnicity (N, % Latino)	7	(23%)	13	(38%)	*p*=.17
Psychotic Disorder Diagnosis (N, %)	3	(10%)	NA		
SIPs Positive Symptoms (mean, +/-SD)	7.1	(6.9)	1.1	(1.6)	*p*<.001
SIPs Negative Symptoms	9.2	(6.4)	1.1	(1.7)	*p*<.001
SIPs Disorganized Symptoms	4.7	(3.7)	0.7	(1.0)	*p*<.001
SIPs General Symptoms	4.9	(5.0)	1.1	(1.4)	*p*=.001
Psychotropic Medication (N, None/Antipsychotics/Anti-depressants)	22/3/6		NA		

Table 2: Structural Magnetic Resonance imaging results of neuroanatomic measures associated with social cognition in 22q11.2 deletion participants versus typically developing controls.

Region of Interest	Hemi-sphere	Volume F	Volume FDR q-value	Volume ↑ or ↓ in 22qDS	Cortical Thickness F	Cortical Thickness FDR q-value	Cortical Thickness ↑or ↓ in 22qDS	Surface Area F	Surface Area FDR q-value	Surface Area ↑ or ↓ in 22qDS
Amygdala	**L**	**5.5**	**.037**	↓						
	R	2.9	.127							
Fusiform	**L**	**9.1**	**.009**		0.7	.500		**12.7**	**.003**	↓
	R	**8.1**	**.013**	↓	**7.1**	**.021**	↑	**24.4**	**<001**	↓
Superior Frontal	L	1.0	.398		2.3	.181		3.8	.083	
	R	0.4	.592		4.9	.051		0.03	.939	
Superior Temporal	L	2.0	.207		4.9	.051		0.02	.950	
	R	**5.1**	**.048**	↓	0.1	.837		**6.6**	**.026**	↓
Insula	**L**	**13.4**	**.003**	↑	**16.1**	**<.001**	↑	4.2	.070	
	R	**22.6**	**<.001**	↑	**24.1**	**<.001**	↑	3.4	.098	
Anterior Cingulate	**L**	**12.4**	**.003**	↓	2.3	.181		**17.1**	**<.001**	↓
	R	**10.6**	**.005**	↓	1.26	.339		**16.6**	**<.001**	↓
Middle Frontal	L	3.9	.077		**16.91**	**<.001**	↑	**13.9**	**.002**	↓
	R	**13.1**	**.005**	↓	**29.16**	**<.001**	↑	**39.6**	**<.001**	↓
Inferior Frontal	L	0.2	.728		**20.84**	**<.001**	↑	0.23	.728	
	R	0.00	.950		**10.13**	**.006**	↑	0.72	.488	
Occipital	**L**	**13.1**	**.003**	↓	**5.04**	**.049**	↑	**34.7**	**<.001**	↓
	R	**8.3**	**.017**	↓	4.42	.064		**25.2**	**<.001**	↓
Orbitofrontal	**L**	**5.9**	**.034**	↑	**16.49**	**<.001**	↑	0.00	.950	
	R	**7.1**	**.021**	↑	**16.36**	**<.001**	↑	0.01	.950	

Study 2: Figures

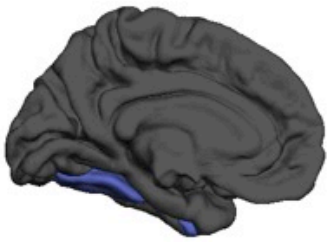
Figure 1: Neuroanatomic regions of interest typically associated with social cognition examined in this study.

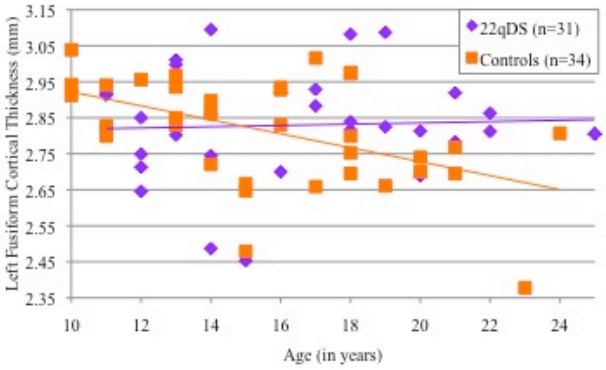


*The occipital cortex was used as a control region.

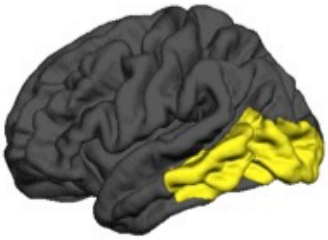
Figure 2: Developmental disruption in cortical thickness in 22q11.2 Microdeletion Syndrome vs. typically developing controls in the fusiform area (A) and occipital cortex (B).

A.





B.



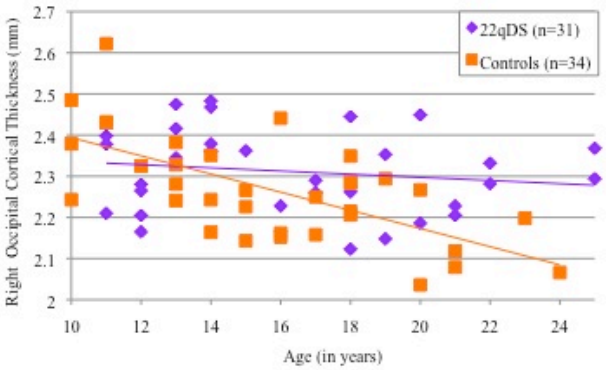


Figure 3: Relationships between the right amygdala and social cognition measures in 22q11.2 Microdeletion Syndrome. Figure 3A: Relationship between right amygdala and performance on The Awareness of Social Inference (Theory of Mind) task. Figure 3B: Relationship between right amygdala and performance on the Penn Emotion Recognition Test. Figure 3C: Relationship between right amygdala and performance on the Penn Emotion Differentiation Test.

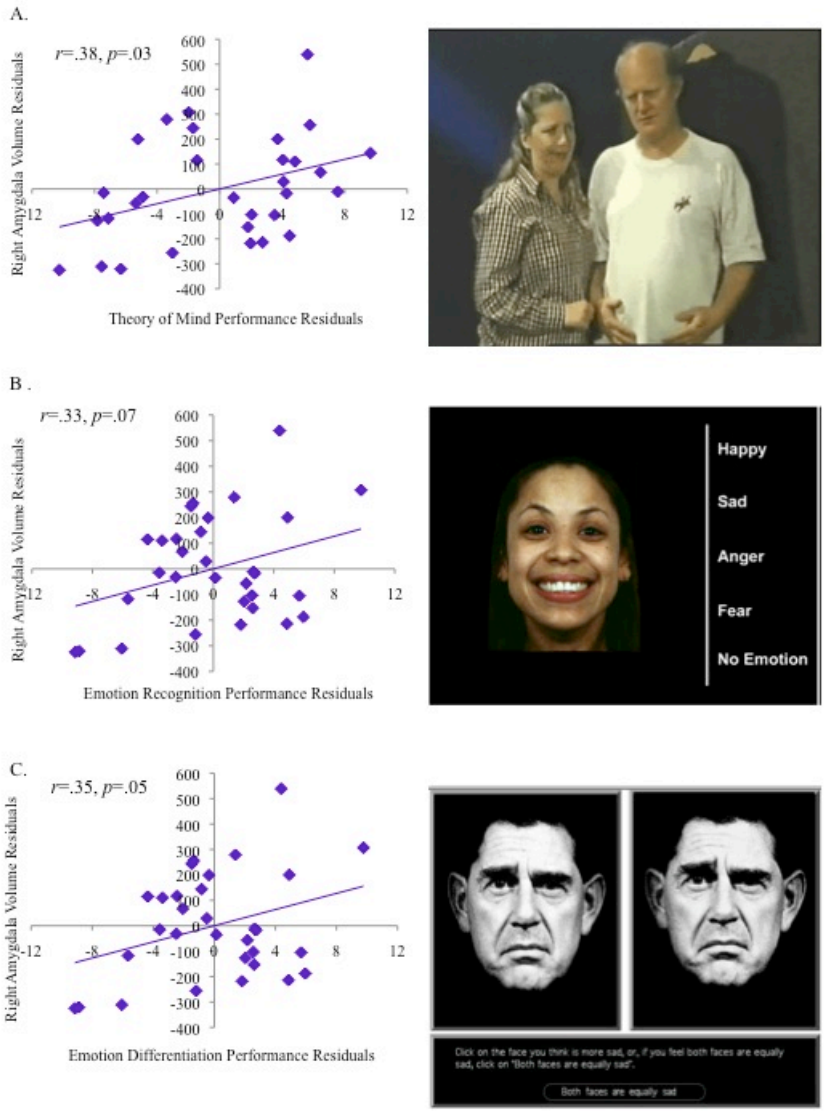
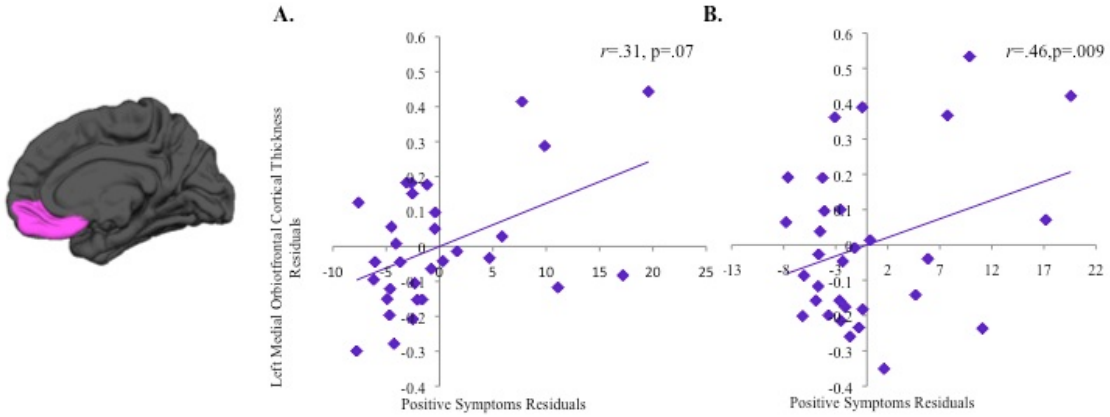


Figure 4: Relationships between the medial orbitofrontal cortices and positive symptoms in 22q11.2 Microdeletion Syndrome



Study 2: Supplemental Materials

Supplemental Table 1: Structural Magnetic Resonance imaging results testing for scanner differences.

		Volume		Cortical Thickness		Surface Area	
Region of Interest	Hemi-sphere	F	p-value	F	p-value	F	p-value
Amygdala	**L**	0.68	.41				
	R	0.09	.77				
Fusiform	**L**	0.42	.52	0.04	.85	0.16	.69
	R	0.45	.50	0.07	.79	0.05	.82
Superior Frontal	L	0.14	.71	0.09	.76	0.22	.64
	R	0.30	.59	0.00	.98	0.29	.60
Superior Temporal	L	0.13	.72	0.72	.40	0.00	.99
	R	0.20	.65	0.14	.71	0.01	.92
Insula	**L**	0.01	.98	1.04	.31	0.19	.67
	R	0.12	.73	0.02	.90	0.17	.68
Anterior Cingulate	**L**	0.30	.58	1.30	.26	0.00	.99
	R	0.43	.52	0.11	.74	0.03	.87
Middle Frontal	L	1.53	.22	0.22	.64	0.95	.34
	R	0.56	.46	0.02	.88	0.33	.57
Inferior Frontal	L	0.01	.94	0.87	.35	0.25	.62
	R	0.01	.93	0.12	.73	0.07	.79
Occipital	**L**	0.08	.79	1.30	.26	0.03	.85
	R	0.07	.79	0.05	.82	0.10	.75
Orbitofrontal	**L**	2.73	.10	0.19	.67	3.07	.09
	R	1.1	.30	0.45	.51	0.65	.42

White Matter Integrity as a Predictor of Psychotic Symptoms in 22q11.2 Microdeletion Syndrome

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Abstract

Introduction: 22q11.2 Microdeletion Syndrome (22qDS) is a highly penetrant genetic mutation associated with a 30-fold increase in risk for psychosis. This disorder is also characterized by inappropriate circuit formation due to aberrant neurodevelopment, suggesting that cerebral dysconnectivity may contribute to symptom development. Here we sought to examine: 1) differences between 22qDS participants and typically developing controls in multiple diffusion tensor imaging (DTI) measures within white matter tracts involved in social cognitive neural circuitry; 2) whether there is an altered age-related trajectory of these white matter pathways in 22qDS; and 3) relationships between DTI measures, social cognition task performance and positive symptoms of psychosis in 22qDS.

Method: DTI data were acquired on 49 participants (26 22qDS, 23 demographically comparable controls, age range: 10-25 years old). All image processing was conducted using FMRIB Software Library (FSL). We applied a non-linear registration approach (Tract-Based Spatial Statistics) to 64-direction DTI data to examine differences between 22qDS vs. typically developing controls in DTI indices of fractional anisotropy (FA), axial (AD) and radial diffusivity (RD), which are believed to reflect white matter integrity, axonal coherence, and myelination, respectively. We investigated regions of interest (ROI's) in the following white matter tracts implicated in social cognitive processes: superior longitudinal fasciculus, uncinate fasciculus, anterior cingulum, inferior longitudinal fasciculus, and inferior frontal occipital fasciculus. The anterior thalamic radiation was investigated as a control region. Social cognition domains assessed were: emotion recognition, emotion differentiation, and Theory of Mind (ToM). Positive symptoms were assessed using the Structured Interview for Prodromal Symptoms (SIPS).

Results: In comparison to typically developing controls, 22qDS participants showed reduced FA in the left inferior frontal fasciculus and right uncinate fasciculus, fiber tracts that connect occipital to the temporal lobes and medial temporal with orbitofrontal regions, respectively. 22qDS participants also had significantly decreased AD in multiple tracts, including the bilateral inferior and superior longitudinal fasciculus (which connects the parietal lobe to the frontal lobes), and the uncinate fasciculus. In contrast, there were no group differences on measures of RD. Greater severity of positive symptoms was associated with decreased AD in the left inferior frontal fasciculus and right superior longitudinal fasciculus, while increased axial diffusivity in the left inferior longitudinal fasciculus was associated with better social cognition in 22qDS. Conclusion: Although the cellular basis of these white matter microstructural alterations remains to be determined, our findings of disproportionate reductions in axial vs. radial diffusivity suggest that, in 22qDS, white matter microstructure dysfunction is driven by axonal damage, not demyelination. These findings additionally provide preliminary evidence that white matter microstructure in tracts relevant to social cognition may be useful endophenotypes to pursue with regard to psychosis risk in 22qDS.

Introduction

22q11.2 Microdeletion Syndrome (22qDS; also known as Velocardiofacial syndrome or DiGeorge Syndrome) is a neurogenetic disorder occurring in approximately 1 out of every 4,000 viable births (Goodship, et al., 1998). 22qDS is caused by a deletion of a segment on the long arm of chromosome 22q11.2, an area that consists of approximately 40 deleted genes, many of which are involved in neuronal processes (Maynard, et al., 2003). Several of these deleted genes are involved in myelination (e.g., PIK4CA, Jungerius, et al., 2008) or axonal growth (e.g., RTN4R, Hsu, et al., 2007), which may be related to aberrant development of white matter in this syndrome. Notably, approximately 30% of young adults and adolescents with 22qDS develop a psychotic disorder (Gothelf, Feinstein, et al., 2007). Therefore, 22qDS represents a unique opportunity to examine how a highly penetrant disorder with well-defined genetic etiology may lead to brain changes that then affect a complex psychiatric phenotype (i.e., psychosis).

It has long been proposed that schizophrenia arises as a disorder of "dysconnectivity," whereby genetic and neurodevelopmental influences lead to structural abnormalities in white matter tracts critical for cerebral communication (for a review, see Karlsgodt et al., 2008). Notably, white matter changes in adolescence parallel the development of cognitive and social – affective processes during this sensitive period, which may be relevant to the development of the disorder. Many of the structural neuroanatomic changes that take place during adolescence occur in brain regions implicated in social cognition (Blakemore, 2008b). Because social cognition is a complex construct requiring integration of multiple brain areas, these processes are likely to be profoundly disrupted by dysfunctional integration among neuronal systems. Thus, examining whether the integrity of white matter pathways connecting "social cognitive" brain structures predicts psychotic symptoms in adolescents and young adults with 22qDS may

advance understanding of the contribution of altered structural connectivity to symptom development, in the context of a genetically homogenous high-risk population.

Diffusion tensor imaging (DTI), which measures the diffusion of water molecules within axons, is one way of examining connectivity between brain regions. Specifically, the degree of fractional anisotropy (FA) in a voxel indicates the directionality and density of the fiber tracts, and can be viewed as a measure of white matter or myelin integrity. FA values fall between zero and one: zero indicates that the diffusion is isotropic, or unrestricted in all directions, indicating an absence of fiber tracts to constrain directionality. A value of one means that diffusion occurs along one axis, suggesting increased white matter integrity. Though FA has been used as a standard measure of "white matter integrity," recent evidence suggests that other DTI indices, such as axial diffusivity (AD) and radial diffusivity (RD) may reveal more about the specific nature of the white matter dysfunction (Alexander, Lee, Lazar, & Field, 2007). For example, AD measures diffusivity along the principal axis, and decreases in AD have been linked with greater axonal damage (Budde, Xie, Cross, & Song, 2009; Song, et al., 2003). RD is an average of the measures of the diffusivities in the two minor axes, and increased RD has been associated with demyelination (Song, et al., 2003; Song, et al., 2002). To our knowledge, only two published studies of 22qDS have examined all three DTI component measures (Kikinis, et al., 2012) (Radoeva, et al., 2012), and none of these have examined the relationship between these measures and psychotic symptoms in 22qDS.

Existing DTI evidence suggests that there is disrupted white matter integrity in multiple brain regions in 22qDS. Two cross sectional studies on children with 22qDS found reduced FA in the superior longitudinal fasciculus (SLF, Barnea-Goraly, et al., 2003; Sundram, et al., 2010), one of the largest long-range fiber tracts in the brain which connects the parietal to frontal lobes,

and one found reductions in the inferior longitudinal fasciculus (ILF, Sundram, et al., 2010), which connects the occipital and temporal lobes. The largest 22qDS DTI study to date (33 22qDS, 16 unaffected siblings, mean age: 18.0 years), found bilateral FA reductions in the uncinate fasciculus, a tract which connects regions of the limbic system with orbitofrontal cortex (Radoeva, et al., 2012), suggesting that white matter pathways connecting regions associated with social cognition may be compromised in 22qDS. In adults with 22qDS, disruption in other white matter tracts has been observed in multiple brain regions, including the parietal (Kikinis, et al., 2012) (da Silva Alves et al., 2011) and parahippocampal regions (da Silva Alves et al., 2011). The disparate pattern of findings in 22qDS suggest that further studies investigating developmental effects on white matter microstructure in 22qDS, with larger sample sizes (most current publications have < 20 individuals with 22qDS in their sample) and multiple DTI indices are warranted, in order to better understand the nature of white matter pathology in 22qDS.

Another reason for these discrepant findings may be due to difficulties encountered when registering DTI data (Smith, et al., 2006), particularly when the shape of tracts differ between a patient and control group. Thus, use of a well-validated nonlinear registration approach, such as Tract Based Spatial Statistics (TBSS), a part of FMRIB Software Library (Smith, et al., 2006), is crucial for obtaining accurate results. In this approach, TBSS first creates an average "skeleton" of the center of all tracts included for all subjects and then projects the center of each subject's data to this skeleton. This methodology guarantees that data analyses are conducted only in regions where data is present for all participants.

There is also newly emerging evidence regarding the relationships between white matter integrity and behavior in 22qDS. For example, in a combined analysis of 22qDS participants and controls, increased axial diffusivity in the posterior corona radiata, SLF, and inferior fronto-

occipital fasciculus was related to better social skills and social functioning (Radoeva, et al., 2012). Regarding psychotic symptoms, Sundram et al. (2010) reported that reduced FA in the posterior limb of the internal capsule was associated with higher schizotypy scores in 22qDS. Additionally, increased psychotic symptom severity as assessed by the Positive and Negative Symptom Scale (PANNS, Kay et al., 1987), was associated with reduced FA in frontal, cingulate, and temporal regions in adults with 22qDS (da Silva Alves, et al., 2011). These findings provide preliminary evidence that disruption of white matter integrity may be relevant to psychotic symptoms in 22qDS. However, no study has examined the relationship between laboratory-based measures of social cognition (e.g., Theory of Mind, emotion processing) and DTI measures in individuals with 22qDS.

Findings from idiopathic schizophrenia may also provide insight into regions associated with social cognition that may be affected in 22qDS. For instance, a similar pattern of FA reduction in the uncinate fasciculus has been identified in individuals at clinical high-risk for developing schizophrenia, as well as first-episode and chronic schizophrenia patients (Burns, et al., 2003; Kawashima, et al., 2009; Szeszko, et al., 2005). Greater severity of positive symptoms has shown to correlate with reduced FA in the uncinate fasciculus and the SLF in patients with idiopathic schizophrenia (Seok, et al., 2007; Skelly, et al., 2008). Taken together, these findings suggest that reduced connectivity between areas involved in social cognition may also be related to psychotic symptomatology.

As such, this study had four main goals: 1) to examine group differences between 22qDS participants and controls on multiple DTI measures (e.g., FA. AD, and RD) in tracts connecting brain regions associated with social cognition, 2) to identify relationships between positive symptoms, social cognition performance and measures of white matter microstructure in 22qDS,

3) to observe whether there are developmental disruptions associated with 22qDS in measures of FA, AD, and/or RD, in comparison to typically developing controls, and 4) as an exploratory analysis, we sought to identify whether the joint contribution of behavioral and DTI measures is a better predictor of positive symptoms in 22qDS, compared to behavioral predictors alone. First, based on previously published research (Radoeva, et al., 2012; Sundram, et al., 2010), we hypothesized that there would be reduced FA in long-range fiber tracts in 22qDS relative to controls, including the SLF and uncinate fasciculus. Based on a recent publication by Radoeva (2012), we hypothesized that these group differences would be driven by AD. Next, we hypothesized that white matter integrity within the uncinate fasciculus, a white matter structure relevant to social cognition and previously shown to be disrupted in both patients with 22qDS and idiopathic schizophrenia (Barnea-Goraley et al., 2003; Szeszko, et al., 2005), would be associated with positive symptom severity.

Methods

Participants

The initial sample consisted of 60 participants (10-25 years old, 30 22qDS and 30 controls). DTI data from 11 participants (4 22qDS, 7 controls) were excluded due to poor image quality or severe motion/scanning artifacts. Thus, the final sample consisted of 49 participants (26 22qDS, 23 controls).

22qDS participants consisted of individuals with a molecularly confirmed diagnosis of 22q11.2 deletion syndrome recruited from an ongoing longitudinal study at the University of California, Los Angeles (UCLA). Healthy controls were also recruited from this study. Exclusion criteria for all study participants were: neurological or medical condition disorder that might affect performance, insufficient fluency in English, and/or if they endorsed substance or

alcohol abuse and/or dependence within the past six months. Controls additionally must not meet criteria for any major mental disorder, with the exception of attention deficit –hyperactivity disorder (ADHD) or past episode of depression, based on information gathered during the Structured Clinical Interview for DSM-IV Axis I Disorders (M. B. First, Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997).

All participants underwent a verbal and written informed consent process. Participants under the age of 18 years provided written assent, while their parent or guardian completed written consent. The UCLA Institutional Review Board (IRB) approved all study procedures and informed consent documents.

Measures

Structured Interview for Prodromal Syndromes

A master's level trained clinician assessed all participants on the positive, negative, disorganized, and general symptom scales from the Structured Interview for Prodromal Syndromes (SIPS; McGlashan, 2001). Symptoms on these scales are rated from 0-6, with zero representing an absence of symptoms and six referring to an extremely severe level of symptoms. This measure has shown excellent inter-rater reliability (above .75, Meyer, et al., 2005; Miller, et al., 2003). All raters demonstrated good inter-reliability for symptom ratings, with kappa values ranging from .85 to 1.00. For the purposes of this study, we used the sum of the positive SIPS symptom scores as separate dimensional measures of psychotic symptoms. This measure encompasses a range of symptom severity, including sub-threshold (prodromal) and fully psychotic symptoms.

Social Cognition Tasks

Study participants received the Penn Emotion Recognition Test (ER40), a computerized emotion identification task in which 40 color photographs of adult faces, varying in race and gender, are randomly presented (Kohler, et al., 2000). Participants were asked to identify the emotion of each face (happy, sad, anger, fear, or no emotion) and were given as long as needed to respond (total maximum score=40, each emotion presented 8 times). Participants also received the Penn Emotion Differentiation Task (EMODIFF), a computerized emotion differentiation task in which individuals are presented with two black and white faces of the same person and are asked to choose which of the two faces displayed expresses an emotion more intensely (e.g., more happy, more sad), or decide that the two faces are equally happy or sad (total maximum score=40) (Erwin, et al., 1992). Both measures have shown adequate construct validity and test-retest reliability (Carter, et al., 2009; Rojahn, et al., 2000), have been widely used in studies with schizophrenia patients (e.g., Butler, et al., 2009; Sachs, et al., 2004; Silver, et al., 2002), as well as in adolescents (Roddy, et al., 2012; Schenkel, et al., 2007).

All participants were administered Part 3 of The Awareness of Social Inference Test (TASIT, McDonald, et al., 2003). The TASIT is a computerized task believed to assess one's ability to comprehend the intentions of others, particularly how one comprehends white lies or sarcasm. The task consists of 16 vignettes (each lasting between 15-60 seconds), eight of which show an individual telling a lie, while the other eight display an interaction in which someone uses sarcasm. After viewing each vignette, an assessor asked the participant four questions related to the scene: 1) what someone is doing to another person in the scene, 2) what someone is trying to say to the other person, 3) what one of the individuals in the scene is thinking, and 4) what one of the characters in the vignette is feeling. After task completion, an overall score was calculated (maximum=64). The TASIT has shown adequate reliability and validity with brain-

injured patients (McDonald, et al., 2006), and has been used with adolescents at clinical high-risk for psychosis, along with first-episode and chronic patients with schizophrenia (M. F. Green, et al., 2011).

Image Acquisition

All scanning was carried out on a Siemens 3 Tesla "Tim Trio" MRI scanner at the Brain Mapping Center at UCLA (22qDS=14, controls=13) or at the Center for Cognitive Neuroscience (22qDS=12, controls=10). Measures of brain structure were obtained with high-resolution structural MRI. T1-weighted anatomical images were acquired with an MPRAGE sequence with the following acquisition parameters: TR/TE/TI = 2300/2.91/900; flip angle = 9 degrees; slice thickness = 1.20 mm, with a 240x256 acquisition matrix. A diffusion-weighted (DTI), spin-echo echo-planar imaging scan was collected using these parameters: 64 directions, TR/TE = 7100/93 ms; FOV=190x190 mm; 96x96 matrix; slice thickness=2.0 mm; b-value = 1000 s/mm^2.

Image Analysis

All image processing was conducted used FMRIB Software Library (FSL). The T1-weighted images were skull-stripped using FSL's Brain Extraction Tool (BET), and then linearly aligned using FSL's "FLIRT" (with 6 degrees of freedom) to a common space (Colin27) with 1mm isotropic voxels and a 220×220×220 voxel matrix. For the DTI scans, we removed non-brain regions from T2-weighted weighted *b0* image with BET and a mask was then applied to the remaining 64 volumes. We then corrected the images for eddy current distortion by using FSL's eddy correct tool. Then, each individual's eddy corrected *b0* image was linearly aligned (9 degrees of freedom) and down-sampled to a version of their corresponding T1 image (110×110×110, 2×2×2mm) that was previously aligned to the Colin27-MNI space. To compensate for EPI-induced susceptibility artifacts, the *b0* map was elastically registered to the

T1 structural scan. We then applied the transformation matrix from the linear alignment of the mean *b0* image to the T1-weighted volume to each of the 64 diffusion-weighted volumes. The original gradient vectors were rotated using the rotation matrix from the linear transformation. FA images were then calculated for each subject using DTIFit (FMRIB's Diffusion Toolbox), which fits a diffusion tensor model at each voxel.

Group maps were then created using FSL's Tract-Based Spatial Statistics (TBSS). TBSS is a rigorous registration approach, which is imperative for comparisons in which tract shape or volume is likely to differ between groups. Because our sample included children, we aligned each FA image to each other and identified the "most representative" scan from our sample and this image was then used as the target image. All images were then aligned to the target FA image through nonlinear registration. All images are merged into a single 4D image and nonlinear registration is used to create an FA "skeleton" based on the center of all of the tracts common to the entire group. Data are then projected from the center of each subject's tracts onto the skeleton for group comparison. This method ensures that statistics are only applied in regions where data exist for all subjects, and maximizes the likelihood that the pooled data originate from the center of a tract in every subject.

Regions of interest (ROIs) were identified and determined based on the John Hopkins University probabilistic tractography atlas (Wakana, et al., 2007) and then customized based on the TBSS skeleton for the current study. The ROIs, which include tracts putatively related to social cognition, included: SLF, uncinate fasciculus, anterior cingulum, ILF, inferior frontal occipital fasciculus. The anterior thalamic radiation was included as a control region, which we did not expect to be related to social cognitive function or positive symptoms. Each subject's FA,

AD, and RD skeleton was masked using each of the ROIs. Then average FA, AD, and RD were calculated and extracted for that segment of the skeleton for each individual.

Statistical Analyses

Statistical analyses were performed using SPSS software v. 21 (Chicago, Illinois) and SAS/STAT software (SAS Institute Inc., Cary, NC, USA). We compared demographic characteristics between groups using independent samples t-tests for continuous variables and chi square test for categorical variables. To test for cross-scanner differences, for all DTI measurements, we first conducted a univariate analysis of covariance (ANCOVA) for each identified region in each hemisphere, with scanner type as the between groups factor and group as a covariate.

All neuroanatomic measures were first examined for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests and transformed appropriately if they violated the assumptions of normality. To compare FA, AD, and RD in 22qDS vs. controls, we conducted an ANCOVA for each identified region in each hemisphere, with diagnosis (22qDS vs. control) as the between subjects factor and sex, age, and scanner location as covariates. Due to the large number of comparisons (36), False Discovery Rate (FDR) q-values were estimated using SAS/STAT software. To determine whether outliers were driving any of our significant differences, these analyses were also re-run with outliers (i.e., DTI values > 3 standard deviations away from the mean DTI measure) removed.

To address whether the relationship between age and DTI measures differed between group, we first examined the visual scatterplots of age vs. all DTI measures. In plots that visually appeared to have possible age*group interactions, we then added age*group interaction terms to the original ANCOVA models for each brain region (in addition to group, age, sex, and scanner

location). This resulted in a total of 5 analyses: FA in bilateral regions of the anterior cingulum, FA in right SLF, AD in right ILF, and AD in left uncinate fasciculus.

To explore the relationships between neuroanatomic variables and positive symptoms and social cognition tasks, we conducted correlation analyses only for regions that showed significant group differences between 22qDS participants and controls. This resulted in 10 correlation analyses investigating relationships between positive symptoms and DTI measures and 30 analyses investigating relationships between social cognition performance and DTI measures in 22qDS patients. First, residuals were calculated from each variable, after regressing out the effects of age and sex. Then, Pearson correlations (corresponding to partial correlations) were conducted between each neuroanatomic brain region with residualized positive symptoms and /or social cognition variables. For this exploratory analysis we did not adjust for multiple comparisons, in order to generate hypotheses for future, larger studies.

To explore the joint predictive value of behavioral and structural connectivity measures to the prediction of positive symptoms in 22qDS, we conducted a linear regression analysis and entered the most significant behavioral predictor we had previously identified (TASIT, Jalbrzikowski, et al., 2012), as well as age, sex, and the DTI measure that showed the most significant association with positive symptoms in 22qDS as predictors, and positive symptoms as the dependent variable. We also ran another separate, linear regression analysis with the behavioral measure (TASIT) and covariates (age and sex) as predictors and positive symptoms as the dependent variable. To compare whether the combined model improved the amount of variance accounted for in positive symptoms in 22qDS, we conducted an R-squared change test between the two models.

Results

As shown in Table 1, 22qDS patient and control groups were matched on all demographic factors (all p-values $\geq$ .22).

Scanner Differences

We found that scanner site had a significant effect on multiple DTI measures, with significant p-values ranging from .038 to < .001 (see Supplementary Materials, Table 1 for more detailed information). Due to the presence of significant scanner differences, all ANCOVAs included scanner site as a covariate.

Group Differences

Results for analyses of group differences between 22qDS vs. controls in measures of FA, AD, and RD are presented in Table 2. FA in the right ILF and left uncinate fasciculus was significantly reduced in 22qDS in comparison to typically developing controls. We also found significant reductions in AD (believed to reflect axonal integrity) in the ILF and SLF, and uncinate fasciculus bilaterally in 22qDS. Additionally, in comparison to typically developing controls, AD in the right anterior cingulum and the left inferior frontal-occipital fasciculus was decreased in 22qDS. However, there were no significant group differences between 22qDS participants and controls on measures of RD, a putative index of demyelination. When all analyses were re-run without the 1 outlier included, all of the above results remained significant and no other results became significant.

*Age*Group Interactions*

None of the age*group interactions in regions of interest for FA (right and left anterior cingulum, right SLF) or AD (right ILF, left uncinate fasciculus) reached statistical significance.

Relationships with Axial Diffusivity and Positive Symptoms in 22q11.2 Deletion Syndrome

Significant relationships were observed between positive symptoms in 22qDS and AD in the left ILF (r=-.51, p=.008, Figure 3A) and right SLF (r=-.43, p=.02, Figure 3B). In both regions, decreased AD, which has been associated with axonal damage (Song, et al., 2003) (Budde, et al., 2009), was associated with greater severity of positive symptoms. Relationships between FA in the right ILF and right uncinate fasciculus did not reach statistical significance.

Relationships with DTI Indices and Social Cognition Measures in 22q11.2 Microdeletion Syndrome

As seen in Figure 5, increased AD in the left ILF was associated with improved performance on the TASIT (r=.40, p=.04), ER40 (r=.57, p=.003), and EMODIFF (r=.46, p=.016). Increased AD in the left inferior-occipital fasciculus was also associated with improved performance on ER40 in 22qDS (r=.58, p=.008). In all cases, the greater the axonal organization (higher AD), the better the social cognition performance in 22qDS. There were no significant relationships with FA and any of the social cognition variables in 22qDS.

Combined Behavioral and Neuroanatomic Predictors of Positive Symptoms in 22q11.2 Deletion Syndrome

When testing the ability of both behavioral and neuroanatomic measures to predict positive symptoms in 22qDS, we first entered the raw score for total correct for the TASIT (along with age and sex as covariates) as the sole predictor of positive symptoms, given that this measure was shown to be our strongest predictor in a prior study (Jalbrzikowski, et al., 2012). This overall model was significant ($F(3,22)=4.81$, p=.01), accounting for 40% of the variance in positive symptoms. When both the TASIT and AD in the left ILF were entered as predictors of positive symptoms in 22qDS in a linear regression model, we found that the overall model was significant ($F(4,21)=4.78$, p=.007), with these two predictors (and covariates of age and sex)

accounting for 48% of the variance in positive symptoms in 22qDS. Within this model, the TASIT (t=-2.64, p=.015, b=-.47) was a significant predictor of positive symptoms, and AD in the left ILF (t=-1.80, p=.08, b=-.31) approached significance. R-squared change test between the two models showed that addition of AD in the left ILF trended towards significance in the ability to predict positive symptoms in 22qDS (R-squared change: 8%, p=.08). These findings suggest that AD in the left ILF marginally adds additional variance to the prediction of positive symptoms in 22qDS, over and above ToM performance alone.

Discussion

Here we investigated structural connectivity within social cognitive networks in youth with 22q11.2 Microdeletion Syndrome (22qDS), a disorder associated with aberrant cortical circuit formation and high risk for psychotic illness. We also sought to identify relationships between DTI measures and positive symptoms and social cognition performance in individuals with 22qDS. Several findings emerged, some of which are novel and others which extend upon the small body of existing DTI literature: 1) in comparison to controls, 22qDS participants had reduced FA, indicating reduced white matter integrity, in the right ILF and right uncinate fasciculus, as well as reduced AD, putatively indexing axonal damage, in multiple white matter tracts associated with social cognition; 2) decreased AD in the left ILF and right SLF was significantly associated with increased severity of positive symptoms in 22qDS; and 3) increased axial diffusivity in the left ILF was associated with better social cognition in 22qDS.

The group differences we observed in FA and AD replicate and extend upon the few existing DTI studies on 22qDS. We found FA reductions in the right uncinate fasciculus in 22qDS, similar to Radoeva and colleagues (2012), who found bilateral reductions in this tract (in 22qDS patients relative to their healthy siblings). We also found reduced FA in the right ILF,

which was also previously reported by another laboratory (Barnea-Goraly, et al., 2003). Given that both previous studies used different methods for data processing and analysis, our convergent findings provide additional support that these two regions have reduced white matter integrity in 22qDS.

We also found that, in comparison to typically developing controls, multiple regions (e.g., bilateral regions of the ILF, SLF, and uncinate fasciculus, right anterior cingulum, and left inferior frontal-occipital fasciculus) exhibited decreased AD in 22qDS. Radoeva and colleagues (2012) found a very similar pattern of results. Kikinis et al (2012) also found decreased AD in the left hemisphere in 22qDS patients relative to controls in a region that included the intersection of multiple tracts. Consistent with both of these studies, we did not find differences between 22qDS participants and controls on measures of RD. Taken together, these findings provide preliminary evidence that disruptions in white matter in 22qDS may be driven by axonal damage (Budde, et al., 2009; Song, et al., 2003), rather than demyelination. Indeed, the NOGO Receptor 1 gene (RTN4R), which falls within commonly deleted region of those with 22qDS, is responsible for the regulation of axonal growth and regeneration after axonal injury (Hsu, et al., 2007). However, further studies in animal models associated with 22qDS are necessary to provide direct support for this possibility.

Importantly, we found that decreased AD in the left ILF and right SLF was related to increased positive symptoms in 22qDS. To our knowledge, this is the first study to observe a relationship between positive symptoms and reduced AD in 22qDS. Unlike a previous publication on 22qDS (da Silva Alves, et al., 2011) and multiple publications in idiopathic schizophrenia (Lee, et al., 2013; Seok, et al., 2007) (Skelly, et al., 2008), we did not find significant relationships between measures of FA and psychotic symptoms. Furthermore,

multiple studies have examined measures of both axial and radial diffusivity in those with idiopathic schizophrenia, which have consistently demonstrated that disruption in white matter microstructure in multiple regions is driven by increased radial, not axial diffusivity, which authors interpret as indicating that white matter dysfunction in idiopathic schizophrenia is driven by demyelination, rather than axonal damage (Lee, et al., 2013; Levitt, et al., 2012; Ruef, et al., 2012; Seal, et al., 2008). This hypothesis is supported by the post-mortem histopathology literature, which shows disturbances in the function and structure of oligodendrocytes, brain cells responsible for the myelination of axons (for reviews see Davis, et al., 2003; Walterfang, Wood, Velakoulis, & Pantelis, 2006). In contrast, animal studies of in 22q11.2 DS mutant mice suggest disruption of axonal integrity, rather than myelin, as the origin of observed white matter abnormalities (Meechan, Maynard, Tucker, & LaMantia, 2010). Thus, as postulated by Kikinis et al (2012), it is possible that white matter pathology associated with psychosis in 22qDS is driven by different neuropathological mechanisms in comparison to idiopathic psychosis. Nevertheless, such perturbations of structural connectivity between brain regions critical for social processing may lead to downstream commonalities in their phenotypic effects.

We also found a consistent pattern of results when looking at relationships between social cognition performance and measures of axial diffusivity in 22qDS. In particular, improved performance on multiple measures of social cognition (i.e., ToM, emotion recognition, and emotion differentiation) was associated with increased AD in the left ILF in 22qDS. These findings suggest that, in 22qDS, the greater the axonal organization in the ILF, which connects the occipital and temporal lobes, the better one's social cognition performance. These findings provide support for the notion that white matter tracts related to psychotic symptoms in 22qDS are also important for social cognitive skills in this population.

To our knowledge, only one other study has examined the relationship between social measures and DTI variables (Radoeva, et al., 2012). When grouping 22qDS participants and controls together, this study found that better social skills (as measured by the socialization subdomain of the Vineland Adaptive Behavior Scales) were significantly related to increased AD in the right hemisphere of the SLF, the posterior corona radiata, and inferior-frontal occipital fasciculus. However, given that there are well known social deficits in 22qDS (Baker & Skuse, 2005), it is important to examine 22qDS participants and typically developing controls separately, to prevent the occurrence of spurious relationships. As such, future studies in much larger samples are warranted in order to determine whether the relationship between indices of white matter microstructure and social cognition performance in 22qDS deviates from that observed in typically developing youth. It should also be noted that all of the AD measures that showed relationships with social functioning in the Radoeva et al. (2012) study also were associated with non-social neurocognitive measures (e.g., executive function). Given the theoretical scope of this paper, we did not examine relationships between white matter microstructure and non-social cognition in 22qDS; however, comprehensive neurocognitive data are currently being collected in our laboratory, and can be examined in relation to white matter pathology in 22qDS.

Contrary to our predictions, we did not find any age-related developmental disruptions in white matter microstructure in those with 22qDS. One reason for the lack of findings may be due to the fact that our sample size was not large enough to detect an age*group interaction. Secondly, established DTI measures may not be equipped to measure the complexity of increased fiber crossing that is hypothesized to occur as one ages. One specific drawback to this methodology is that, within one voxel, the DTI can only calculate one direction of diffusion,

despite the fact that there are many axons within a voxel (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Pierpaoli, et al., 2001). For example, if one measures FA in a region that has many different fibers crossing in many different directions, DTI takes the mean of the primary direction; thus, these fibers may "cancel" each other out and reduce the FA of this region, even if FA is high in these different crossing fibers. Thus, with increasing age it is possible that controls are developing a more complex pattern of fiber crossing than those with 22qDS. However, the limitations in current methodology make it difficult to test this hypothesis. Other types of methodologies, such as q-ball imaging, measure diffusion without making assumptions about the underlying white matter microstructure (Tuch, Reese, Wiegell, & Wedeen, 2003). However, this imaging technique prolongs scan time, which is not always feasible for use with clinical populations. Therefore, our collaborators at the Laboratory of Neuroimaging at UCLA are working on developing advanced DTI techniques to quantify the complexity of fiber crossing. Given that many of the regions associated with social cognition continue to develop into adolescence and early adulthood (e.g., SLF and uncinate fasciculus, Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008) and given that psychosis often develops during adolescence (Paus, et al., 2008), these regions may show age-related developmental disruptions in 22qDS which could be detected with these newly developing methods.

There are several limitations to this study, which should be noted. First, given the cross-sectional design we were unable to investigate baseline DTI measures or change in these measures over time as predictors of subsequent development of psychotic symptoms in 22qDS. In the future, it will be critical to incorporate a longitudinal approach, particularly given that other studies looking at structural neuroanatomic predictors of psychosis have found change over time to be a strong predictor of symptom development, in both 22qDS (Kates, Antshel, et al.,

2011) and idiopathic psychosis (Sun, et al., 2009; Takahashi, et al., 2009). Second, DTI is an imaging technique that is more susceptible to artifacts than other imaging methodologies, resulting in the loss of 11 participants from our original sample. Finally, the relationships with positive symptoms and social cognition measures were considered exploratory, and thus were not corrected for multiple comparisons. However, given our relatively modest sample size we chose to be less stringent and leave open the possibility for a Type I error, rather than neglect to report upon a potentially relevant finding. Indeed, the finding that AD in the left ILF was associated with both social cognition and positive symptoms in 22qDS suggests that this may be an important finding to follow up in larger-scale future studies.

The current study sets a foundation for the development of future multi-modal predictive studies in 22qDS. Given that these white matter pathways connect to gray matter regions associated with social cognition, in order to better understand how neuropathophysiological mechanisms are related to social impairment in 22qDS, it will be important to examine relationships between measures of structural white matter connectivity and gray matter thickness, and in turn, how these measures related to behavior, in both healthy individuals and those with 22qDS. Furthermore, in the future, it will also be important to examine how white matter microstructure in 22qDS is related to genetic pathways, particularly since multiple genes within the deleted region are associated with neuronal development (Maynard, et al., 2003). Specifically, well-validated bioinformatics approaches (e.g., Weighted Gene Coexpression Network Analysis, Zhang & Horvath, 2005) have been developed, allowing us to identify pathways or modules of gene expression related to psychosis in 22qDS patients, and relate these molecular features to neuroimaging and clinical data, thus connecting genes to brain to behavior, and setting up future studies to more thoroughly assess causality and mechanism both in humans

and in animal models.

Findings from this study continue to shape and build upon the existing literature on DTI in 22qDS. Although the cellular basis of these white matter microstructural alterations remains to be determined, our findings of disproportionate reductions in axial vs. radial diffusivity suggest that, in 22qDS, white matter microstructure dysfunction is driven by axonal damage, rather than demyelination. Our results also provide preliminary evidence that axonal integrity in the ILF is related to both positive symptoms and social cognition ability in 22qDS, suggesting that white matter pathology in this region may be a useful endophenotype to pursue in regards to identifying psychosis risk, particularly in the context of this recurrent genetic mutation. While it is not known whether similar patterns are seen in youth at clinical high risk for psychosis, the identification of risk endophenotypes in this genetically homogeneous subgroup may also shed light on the pathophysiology of psychotic illness in the broader population.

Table 1:Demographic and Clinical Characteristics of Study Participants

	22qDS Participants (n=26)	**Healthy Comparison Participants (n=23)**	
Age (years, +/- SD)	16.4 (4.0)	15.4 (3.0)	.38
Participant Education (years,+/- SD)	8.6 (3.9)	9.3 (3.3)	.51
Parental Education (years,+/- SD)	16.5 (2.5)	15.9 (3.0)	.49
Gender (N, % female)	16 (55%)	11 (48%)	.34
Race (Asian/African American/ Caucasian/Multiple)	0/1/23/2	1/2/16/4	.38
Ethnicity (N, % Latino)	6 (23%)	9 (39%)	.22
Psychotic Disorder Diagnosis (N, %)	3 (11%)	N/A	
SIPs Positive Symptoms (mean, +/- SD)	7.2 (7.4)	0.8 (1.4)	*<.001*
SIPs Negative Symptoms	9.1 (6.8)	1.2 (1.9)	*<.001*
SIPs Disorganized Symptoms	4.3 (3.8)	0.6 (0.9)	*<.001*
SIPs General Symptoms	4.6 (5.1)	1.0 (1.5)	*.002*
Psychotropic Medication (N, None/Antipsychotics/Anti-depressants)	3/7/16	N/A	

Table 2: Diffusion tensor imaging results for white matter tracts associated with social cognition in participants with 22q11.2 deletion syndrome versus typically developing controls.

Region of Interest	Hemi-sphere	**Fractional Anisotropy** F	FDR q-value	↑ or ↓ in 22qDS	**Axial Diffusivity** F	FDR q-value	↑or ↓ in 22qDS	**Radial Diffusivity** F	FDR q-value	↑ or ↓ in 22qDS
Anterior Thalamic Radiations	L	0.36	.78		0.17	.81		0.94	.55	
	R	0.54	.70		0.17	.81		0.00	1.00	
Anterior Cingulum	L	0.06	.90		5.31	.07		1.45	.46	
	R	2.76	.22		**13.53**	**.005**	↓	0.00	1.00	
Inferior Longitudinal Fasciculus	L	3.63	.14		**24.07**	**.0002**	↓	0.60	.69	
	R	**6.50**	**.05**	↓	**20.31**	**.0005**	↓	0.21	.81	
Inferior Frontal-occipital Fasciculus	L	5.05	.07		**11.23**	**.009**	↓	0.25	.81	
	R	0.99	.55		5.77	.066		0.00	1.00	
Superior Longitudinal Fasciculus	L	3.84	.13		**26.74**	**.0002**	↓	0.34	.78	
	R	1.41	.46		**17.11**	**.0009**	↓	1.17	.51	
Uncinate Fasciculus	L	5.68	.07		**19.52**	**.0005**	↓	0.04	.92	
	R	**7.66**	**.03**	↓	**20.20**	**.0005**	↓	0.15	.81	

Figure 1: White matter pathways connecting neuroanatomic structures involved in social cognition examined in this study. Fractional anisotropy, axial diffusivity, and radial diffusivity measures were calculated for the anterior cingulum (yellow), the superior longitudinal fasciculus (green), the inferior fronto-occipital fasciculus (red), the inferior longitudinal fasciculus (dark blue) and the uncinate fasciculus (light blue). The anterior thalamic radiations (not shown) was used as a control region.

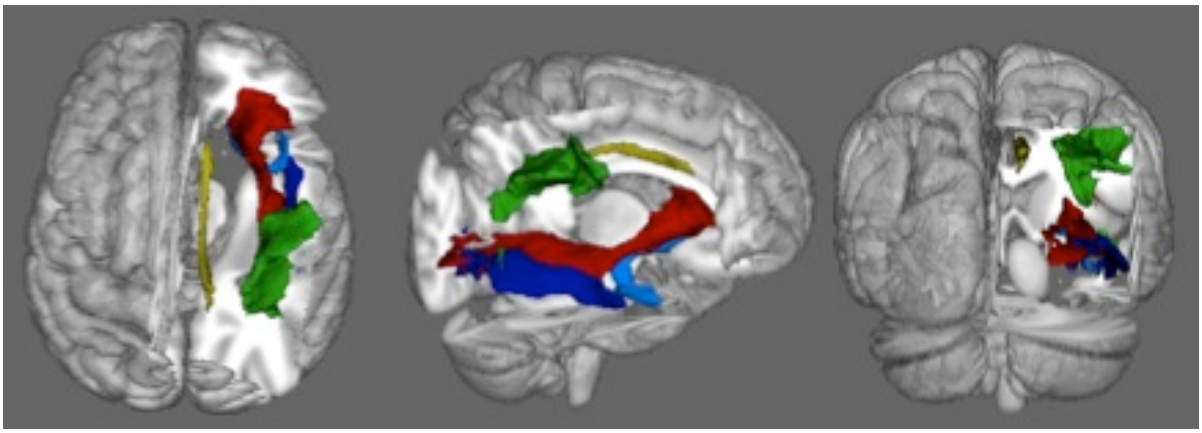
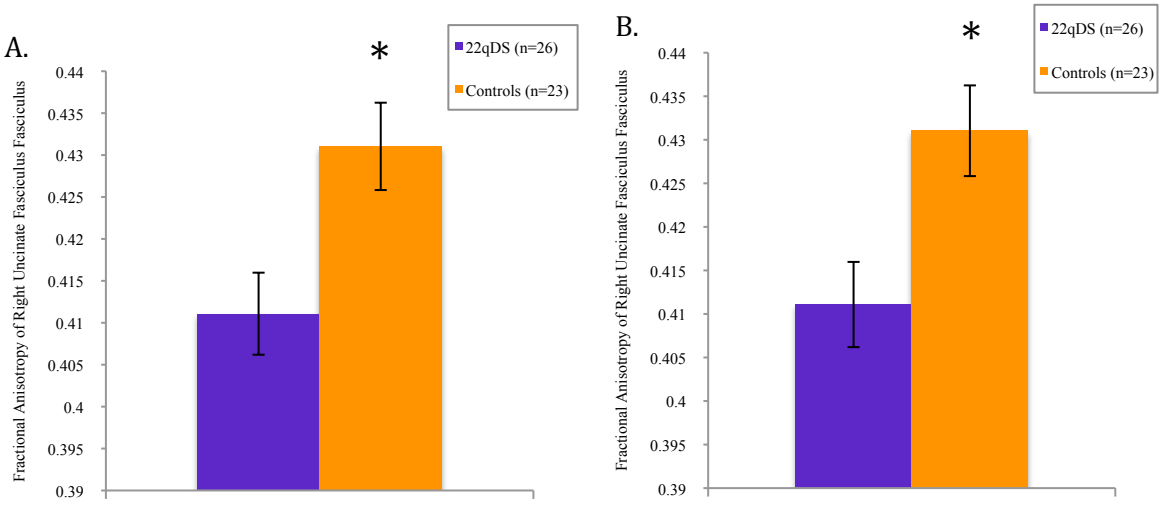
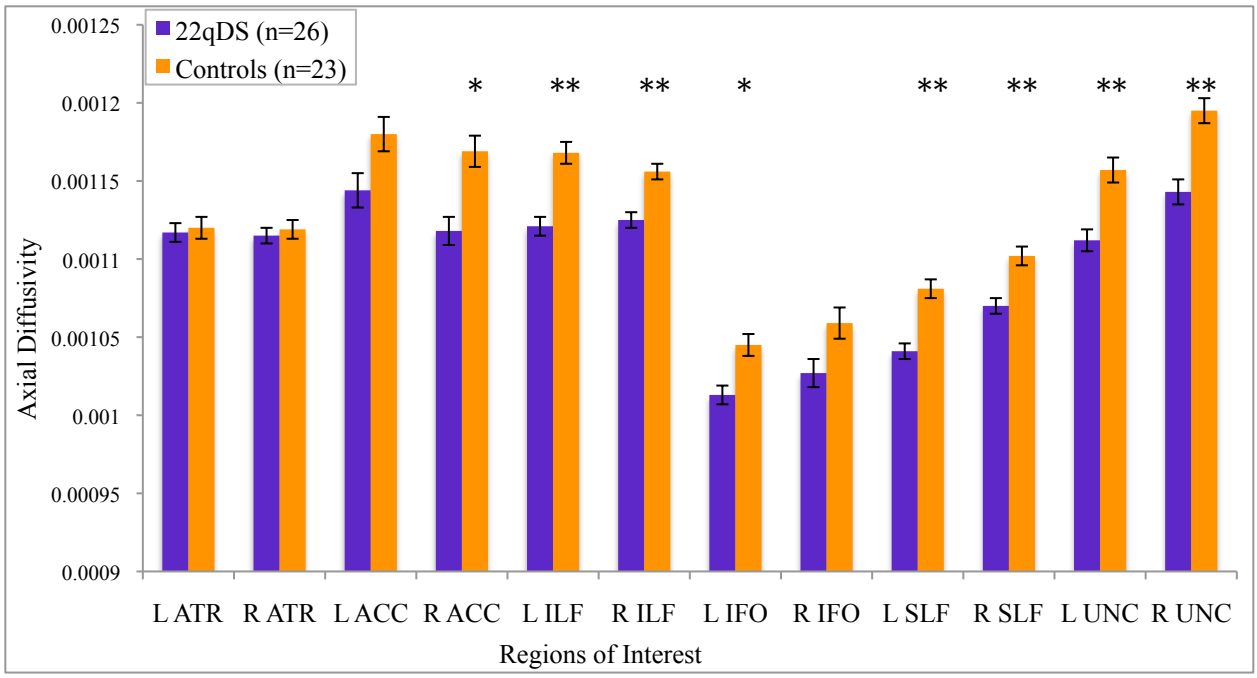


Figure 2: Group differences between individuals with 22q11.2 Microdeletion Syndrome versus typically developing controls on measures of fractional anisotropy in the A) right inferior longitudinal fasciculus and B) right uncinate fasciculus. Fractional anisotropy values are marginal means adjusted for covariates of scanner site, age, and gender.



*$p \leq .05$

Figure 3: Group differences between individuals with 22q11.2 Microdeletion Syndrome versus typically developing controls on measures of axial diffusivity (AD). AD values are marginal means adjusted for covariates of scanner site, age, and gender.



L= left, R=right, ATR=anterior thalamic radiations, ACC=anterior cingulum, ILF=inferior longitudinal fasciculus, IFO= inferior fronto-occipital fasciculus, SLF=superior longitudinal fasciculus, UNC= uncinate fasciculus

*p<.01

**p<.005

Figure 4: Relationships between axial diffusivity in the left inferior longitudinal fasciculus and right superior longitudinal fasciculus and positive symptoms in 22q11.2 microdeletion syndrome.

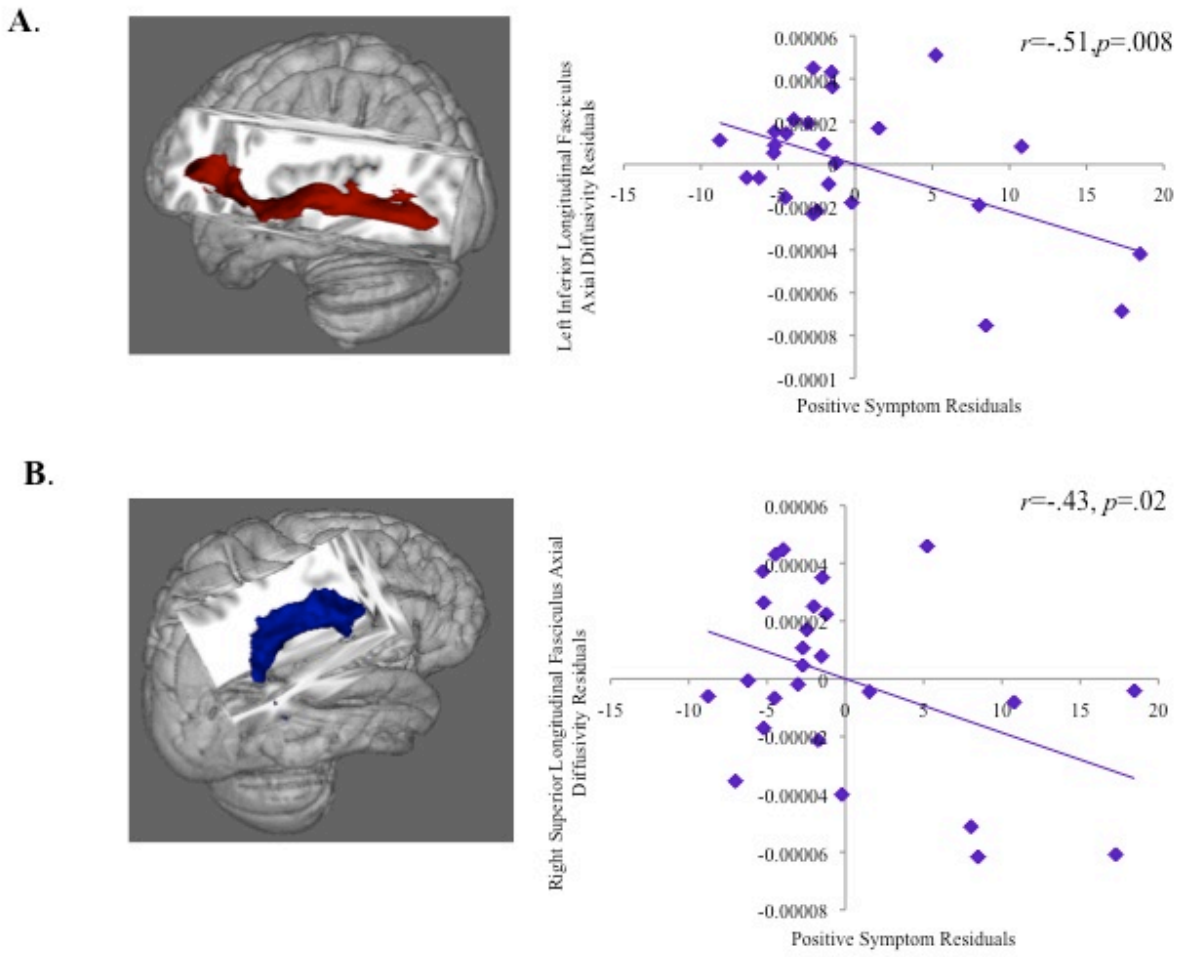
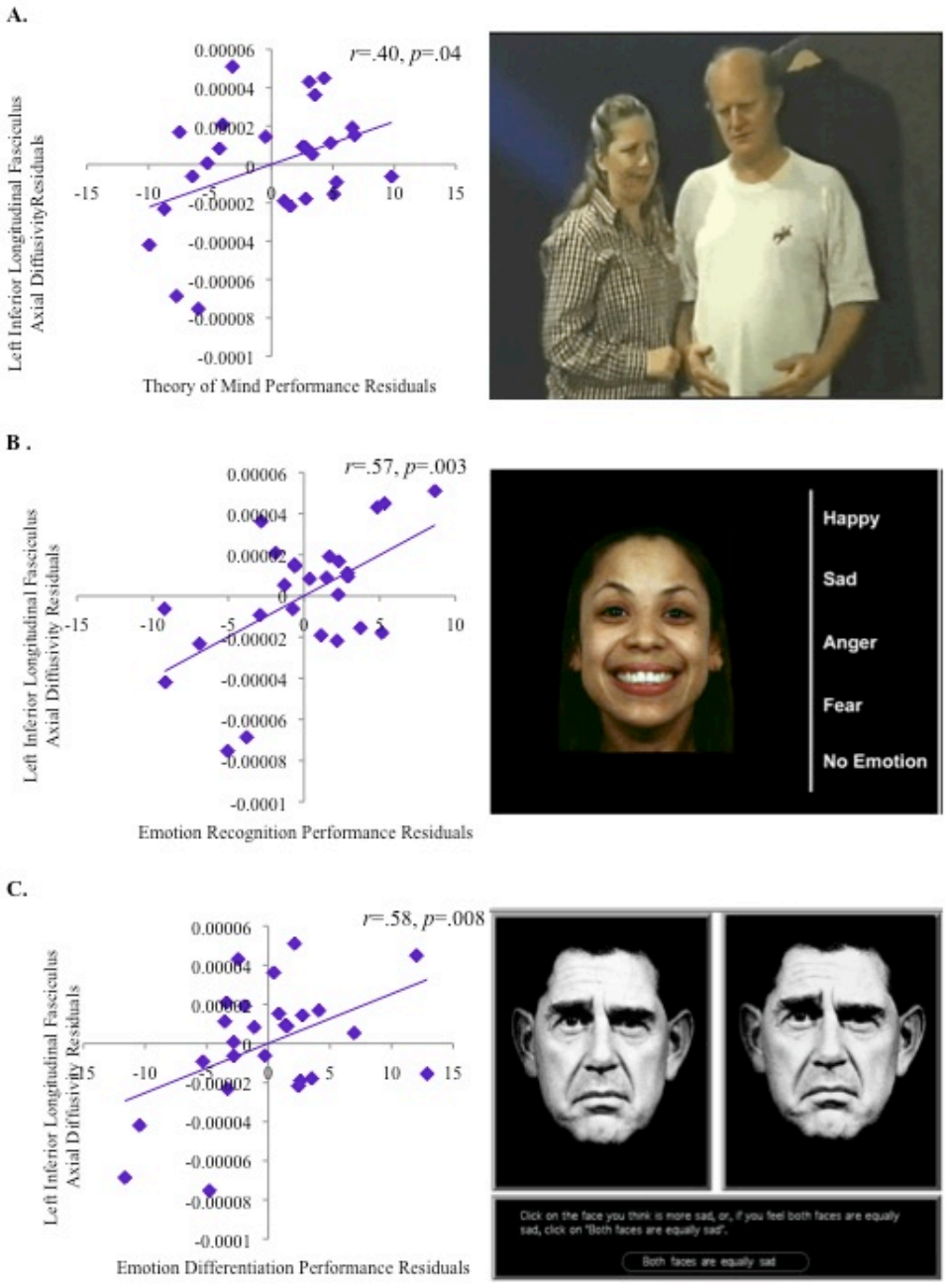


Figure 5: Relationships between axial diffusivity in the left inferior longitudinal fasciculus and Theory of Mind (A), emotion recognition (B), and emotion differentiation (C) performance in 22q11.2 microdeletion syndrome.



Supplementary Materials

Table 1: Scanner differences in measures of fractional anisotropy, axial diffusivity, and radial diffusivity. Comparisons were made between the two scanner sites: Brain Mapping Center (BMC) and Center for Cognitive Neuroscience.

		Fractional Anisotropy			Axial Diffusivity			Radial Diffusivity		
Region of Interest	Hemi-sphere	F	*p*-value	↑ or ↓ in BMC scanner	F	*p*-value	↑ or ↓ in BMC scanner	F	*p*-value	↑ or ↓ in BMC scanner
Anterior Thalamic Radiations	L	**12.43**	**.001**	↑	**11.74**	**.001**	↓	**20.78**	**<.001**	↓
	R	**37.8**	**<.001**	↑	**24.67**	**<.001**	↓	**79.54**	**<.001**	↓
Anterior Cingulum	L	1.69	.2		1.23	.273		**7.135**	**0.01**	↓
	R	1.67	.2		**7.39**	**.009**	↓	**9.06**	**0.004**	↓
Inferior Longitudinal Fasciculus	L	**5.84**	**.02**	↑	0.069	.794		**4.59**	**0.038**	↓
	R	**12.7**	**.001**	↑	3.4	.072		**17.85**	**<.001**	↓
Inferior Frontal Occipital Fasciculus	L	2.37	.131		0.025	.874		1.945	0.17	
	R	1.84	.182		0.419	.521		0	1	
Superior Longitudinal Fasciculus	L	0.93	.339		3.14	.083		3.18	0.081	
	R	**5.15**	**.028**	↑	**12.3**	**<.001**	↓	**19.01**	**<.001**	↓
Uncinate Fasciculus	L	**7.62**	**.008**	↑	0.39	.538		**10.31**	**0.002**	↓
	R	24.91	**<.001**	↑	**5.13**	**.028**	↓	**29.48**	**<.001**	↓

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