Published in final edited form as:

Schizophr Res. 2012 December ; 142(0): 99–107. doi:10.1016/j.schres.2012.10.007.

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, abstract reasoning, working memory, and processing speed. Positive and negative symptoms were measured using scores obtained from the Structured Interview for Prodromal Symptoms (SIPS). 22qDS

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Conflicts of Interests Ms. Jalbrzikowski, Ms. Carter, Dr. Senturk, Ms. Chow, Ms. Hopkins, Dr. Green, Dr. Galván, Dr. Cannon, and Dr. Bearden report no biomedical financial interests or potential conflicts of interest.

Contributors Dr. Bearden 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 first draft of this 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.

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.

Keywords

22q11.2 Microdeletion Syndrome; social cognition; schizophrenia; prodromal; 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 et al., 2007a), making this syndrome one of the largest known genetic risk factors for schizophrenia (Karayiorgou et al., 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 et al., 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 et al., 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 and Gould, 2003). Social cognitive deficits have been consistently found in individuals with schizophrenia across a range of measures (e.g., Corrigan and Toomey, 1995; 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 et al., 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 et al., 1989; Herbener et al., 2005; Novic et al., 1984), as well as in the prodromal period (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 et al., 2007b; Irani et al., 2006; Surguladze et al., 2012); but see also (Bolte and 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 and 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 and Skuse, 2005; Debbané et al., 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, 2008). 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, 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

2.2a 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.

2.2b 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 (Green et al., 2011).

2.2c 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 et al., 2007; Gur et al., 2007a; Snitz et al., 2006). Visuospatial reasoning was also examined, because 22qDS is typically characterized by relative weakness in visuospatial abilities (Bearden 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 nonverbal abstract reasoning, 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 et al., 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,

nonverbal abstract reasoning, 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 then 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, with 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 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 et al., 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 corrected with higher levels of schizotypy symptoms (Baker and 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 et al., 2007b; Kates, 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 and 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 relation 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 et al., 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 et al., 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 and 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, 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 psychosis 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the participants and their families for being a part of our research. We would also like to thank Ms. Chelsea Gilbert, Dr. Sarah Marvin, and Dr. Laurie Brenner, who assisted in conducting clinical assessments and administering neuropsychological measures to our participants.

Role of Funding Sources Funding for this study was provided by National Institute of Mental Health grant RO1 MH085953 (CEB). Funding was also provided by the NIH/NIMH 5T32MH073526-05 (Training Grant in Neurobehavioral Genetics) and Heyler Meyer Research Award given to Ms. Jalbrzikowski. These funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Abbreviations

22qDS	22q11.2 Microdeletion Syndrome
CHR	Clinical high risk
ToM	Theory of Mind
SIPS	Structured Interview for Prodromal Syndromes
STG	superior temporal gyrus
EMODIFF	Penn Emotion Differentiation Task
ER40	Penn Emotion Recognition Task
TASIT	The Awareness of Social Inference Task

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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 red; non-social cognition tasks are in blue. 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.

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	
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	9.8	(6.9)	1.1	(1.7) $p<.001$
SIPs Disorganized Symptoms	5.7	(4.0)	0.6	(0.9) $p<.001$
SIPs General Symptoms	5.4	(4.3)	1.0	(1.3) $p<.001$
Psychotic Symptoms (Positive + Negative Symptoms on SIPs)	19.0	(12.3)	2.2	(2.9) $p<.001$
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-test	p-value	Cohen's <i>d</i>
Non-social Cognition					
Verbal Knowledge					
Vocabulary	37.2 (10.3)	57.8 (12.6)	$t(59)=6.9$	$p<.001$	1.8
Visuospatial Skills					
Matrix Reasoning	14.6 (7.5)	26.9 (5.0)	$t(59)=7.6$	$p<.001$	1.9
Short-Term Working Memory					
University of Maryland Letter Number Sequencing	8.8 (4.1)	15.6 (3.5)	$t(59)=6.9$	$p<.001$	1.8
Processing Speed					
Brief Assessment of Cognition in Schizophrenia Symbol Coding	36.9 (11.4)	59.9 (15.2)	$t(59)=6.7$	$p<.001$	1.7
Social Cognition					
Emotion Recognition					
Penn Emotion Recognition Task	28.7 (4.8)	32.7 (4.4)	$t(59)=3.4$	$p=.001$	0.9
Emotion Differentiation					
Penn Emotion Differentiation Task	17.7 (7.0)	25.7 (6.3)	$t(59)=4.7$	$p<.001$	1.2
Theory of Mind					
The Awareness of Social Inference Test	41.9 (5.0)	54.0 (5.7)	$t(59)=8.9$	$p<.001$	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.

	22q11.2 Participants			Control Participants			Fisher r-to-z test for Equality of Correlations		
	r	p	d	r	p	d	Z	p	
Non-social Cognition									
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	
		F (df)	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-test	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-value	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-value	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