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# Social cognition in 22q11.2 microdeletion syndrome: Relevance to psychosis?

Maria Jalbrzikowski [a], Chelsea Carter [a], Damla Senturk [b], Carolyn Chow [c], Jessica M. Hopkins [a], Michael F. Green [c,d], Adriana Galván [a], Tyrone D. Cannon [a,c], Carrie E. Bearden [a,c,*]

[a] Department of Psychology, University of California, Los Angeles, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095-1563, United States
[b] Department of Biostatistics, School of Public Health, University of California, Los Angeles, CA 90095, United States
[c] Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, 760 Westwood Plaza, Los Angeles, CA 90095, United States
[d] VA Greater Los Angeles Healthcare System, VISN22 Mental Illness Research, Education, and Clinical Center, 11301 Wilshire Blvd., Los Angeles, CA 90073, United States

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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 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 (Murphy et al., 1999; Bassett et al., 2003). 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., Green et al., 2012; Corrigan and Toomey, 1995; Kohler et al., 2000; Inoue et al., 2006). Particularly marked deficits have been identified in the domains of emotion processing (i.e., the ability of schizophrenia

*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.

* Corresponding author at: UCLA Psychiatry & Biobehavioral Sciences, Box 956968, 300 Medical Plaza, Rm 2267, Los Angeles, CA 90095-6968, United States. Tel.: +1 310 206 2983; fax: +1 310 794 9517.
*E-mail address:* cbearden@mednet.ucla.edu (C.E. Bearden).

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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 (Novic et al., 1984; Gessler et al., 1989; Bediou et al., 2005; Herbener et al., 2005), as well as in the prodromal period (Green et al., 2012), 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 (Irani et al., 2006; Gur et al., 2007b; Eack et al., 2010; 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 (Swillen et al., 1997; Woodin et al., 2001; Kiley-Brabeck and Sobin, 2006). 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; Debbane 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). Another study by the same research group found that, in comparison to healthy controls, adolescents with 22qDS displayed a 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 ToM in 22qDS, youth with the disorder 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 a 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., 2012), we hypothesized that those with 22qDS will have a 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 that 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 et al., 2002).

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 to 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, Miller et al., 2003; Meyer et al., 2005). 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 subthreshold (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