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Predicting Social Functioning in Young Adults with 22q11.2 Deletion Syndrome: A Longitudinal Study

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Abstract

Background: The primary objectives of the current study were to (a) describe social functioning outcomes over a 9-year span in individual with 22q11.2 Deletion Syndrome (22q11.2DS) and (b) identify childhood predictors of social functioning in young adults with 22q11.2DS.

Method: Using data from a prospective longitudinal study, young adult social functioning was compared among individuals with 22q11.2DS, their siblings, and community controls. Childhood cognitive, emotional, and behavioral predictors of young adult social functioning were examined. In addition, the relationship between psychosis and social functioning was explored. Family environment and factors contributing to parental stress in adolescence were investigated as potential mediators of the relationship between significant childhood variables and adult social functioning.

Results: Parents rated young adults with 22q11.2DS as having more impaired social functioning than controls. Parent rated childhood internalizing symptoms significantly predicted young adult social functioning in 22q11.2DS, even after controlling for concurrent positive symptoms of psychosis. Problem behaviors contributing to parenting stress in adolescence partially mediated the relationship between child internalizing symptoms and young adult social functioning in 22q11.2DS.

Conclusions: These findings highlight child internalizing symptoms and adolescent problem behaviors as potential targets for social functioning interventions designed to prevent / remediate impairments in 22q11.2DS.

Keywords: social functioning, 22q11.2 Deletion Syndrome (22q11.2DS), developmental delay, internalizing, longitudinal

Predicting Social Functioning in Young Adults with 22q11.2 Deletion Syndrome: A Longitudinal Study

By

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Predicting Social Functioning in Young Adults with 22q11.2 Deletion Syndrome: A Longitudinal Study

22q11.2 deletion syndrome (22q11.2DS) is a genetic disorder caused by a deletion of approximately 40 genes at region q11.2 of chromosome 22. As the most common microdeletion syndrome, 22q11.2DS has a prevalence of approximately 1 in 1,000-4,000 live births (Botto et al., 2003; Grati et al., 2015). The physical phenotype associated with 22q11.2DS is highly variable and involves multiple organ systems. Some of the most characteristic phenotypic traits in 22q11.2DS include cardiac malformations, palatal abnormalities, and facial anomalies (Shprintzen, 2000). An increased risk for psychiatric disorders, including attention deficit / hyperactivity disorder (ADHD), anxiety disorders, mood disorders, autism spectrum disorder (ASD), and schizophrenia has been reported in this population (Antshel et al., 2007; Feinstein, Eliez, Blasey, & Reiss, 2002; Schneider et al., 2014). Notably, about one third of individuals with 22q11.2DS develop schizophrenia, which is much higher than the 0.30% - 0.70% prevalence rate in the general population (American Psychiatric Association, 2013; Drew et al., 2011). Despite the high prevalence of learning disabilities and mild intellectual disability in individuals with 22q11.2DS, the cognitive phenotype for 22q11.2DS consists of both relative strengths and weaknesses. Areas of relative strength include reading decoding, spelling, and rote auditory/verbal memory skills (Antshel, Fremont, & Kates, 2008). In contrast, mathematics, executive functions, visual/spatial memory and attention are areas of relative weakness (Antshel et al., 2008). Individuals with 22q11.2DS often have higher verbal IQ scores than performance IQ scores (Jacobson et al., 2010).

Executive Functions

Executive functions are an area of both relative and normative weakness for individuals

with 22q11.2DS (Antshel et al., 2008). Executive functions are cognitive processes subserved largely by the prefrontal cortex that control behaviors necessary for adapting to novel situations and completing complex tasks when a previous schema of action is unavailable (Carpenter, Just, & Reichle, 2000; Welsh & Pennington, 1988). Although executive functioning is a commonly referenced term in research, there is not uniform agreement about how best to define the construct and which theoretical model best explains the executive processes (Packwood, Hodgetts, & Tremblay, 2011). Early models of executive functioning suggest it is unitary system responsible for all complex cognitive processes, but more recent theoretical models use a multi-component system to explain executive functions (Packwood et al., 2011). Using the theoretical framework with the most empirical support (Packwood et al., 2011), we operationalize executive functioning as a multiple component system characterized by separate but related cognitive processes that can be empirically measured using behavioral paradigms (Miyake & Friedman, 2012). This multi-component system includes (a) the ability to maintain and manipulate information from memory (working memory), (b) the ability to suppress impulses (response inhibition), (c) the ability to change behavior in response to new information (cognitive flexibility) and (d) the ability to formulate a strategy to achieve a goal (planning). While a number of cognitive processes are subsumed under the umbrella of executive functions, these four are the most consistently included cognitive processes included in executive function theories (Miyake et al., 2000; Pennington & Ozonoff, 1996).

Snyder, Miyake, and Hankin (2015) reviewed the current state of research in executive functions related to psychopathology and noted that isolating specific subcomponents of executive functioning is a difficult task because many neuropsychological measures require more than one aspect of executive functioning for successful task completion. Since executive

functioning is both challenging to define (Jurado & Rosselli, 2007) and the constructs are difficult to isolate, we sought to be as inclusive as possible in examining subcomponents of executive functioning and included the four most common of these subcomponents.

Since novel situations are quite common, it is generally well accepted that executive functions regulate many behaviors used to achieve goals in real-world situations (Altgassen & Kliegel, 2014). Therefore, an individual's executive functioning abilities can have social implications; the components of executive functioning (working memory, behavioral inhibition, cognitive flexibility, and planning) are necessary in many social situations. For example, executive functions can regulate a variety of thoughts and behaviors relevant to social situations, such as our ability to make decisions and evaluate risks and consequences, inhibit our impulses, plan for future events and manage novel situations (Miyake & Friedman, 2012).

Social Functioning

Just as there are a variety of ways to operationalize executive functioning, there are a variety of terms used to define social functioning (Cook & Oliver, 2011). For example, in the extant literature, social functioning has referred to a wide variety of constructs including social problems, social skills and occupational functioning. This lack of a clear operationalized definition of social functioning is likely a function of the variety of instruments designed to measure this construct being used in research (and vice versa). Different social functioning domains that have been reported in the literature include activities of daily living, recreational activities, friendships, intimate relationships, employment or occupation, social behaviors, and independence competency. One definition of social functioning is, "one's ability to initiate, form and maintain social relationships with others" (e.g., making friends, playing with others on the playground, attending social events with others) (Campbell, McCabe, Melville, Strutt, & Schall,

2015). Social functioning can also be defined as, "an individual's ability to adapt to and derive satisfaction from his/her social roles (e.g., interaction with friends, coworkers) (Weissman, 1999). What these two definitions have in common, and what our operational definition of social functioning includes, is the individual's ability to make and maintain friendships as well as their satisfaction with these social relationships. More specifically, social functioning can be measured by examining an individual's interpersonal relationships, social activities, and coping in social situations (Sparrow, Cicchetti, & Balla, 2005). Although researchers in this field may use more broad definitions of social functioning and a variety of instruments to measure this construct, we plan to be as inclusive as possible when reviewing the literature for hypothesis generation.

A valid measure of social functioning would likely not include scales that measure social skills, a closely related construct often used interchangeably with social functioning in a rather imprecise fashion. Simply having the social skills does not guarantee that the skills will be deployed or lead to successful social relationships. Social skills are distinct from social functioning and are defined as, "behaviors learned to facilitate awareness of one's social environment and social contingencies, and to be able to solve social problems" (Gillis & Butler, 2007).

Social functioning is an important variable to study, yet thus far, has received scant attention by 22q11.2DS researchers. This is unfortunate as peer rejection or low acceptance among peers in childhood is related to many other childhood problems such as poor academic achievement (Ladd, Kochenderfer, & Coleman, 1996), loneliness and depressed mood (Boivin, Hymel, & Bukowski, 1995) and an increased risk for peer victimization (Hodges, Malone, & Perry, 1997). Peer relationship problems or a lack of friendships in childhood also longitudinally predicts dropping out of school and criminal incidents (Parker & Asher, 1987), as well as

predicting life adjustment and perceptions of self-worth in adulthood (Bagwell, Newcomb, & Bukowski, 1998). Lastly, given that poor social functioning in childhood is a predictor of psychosis in adulthood (Lauronen et al., 2007) and individuals with 22q11.2DS are at an increased risk for schizophrenia (Drew et al., 2011), social functioning is an important variable for further investigation in this population.

Social functioning in 22q11.2DS. Children with 22q11.2DS are significantly more socially inhibited and withdrawn than their peers (Schonherz et al., 2014; Swillen et al., 1997) and demonstrate more problem behaviors (e.g., internalizing behaviors) that interfere with social functioning than their peers (Shashi et al., 2012). Parents of children with 22q11.2DS do not report a delay in early social developmental milestones (Roizen et al., 2007). Instead, social challenges in 22q11.2DS manifest typically in middle childhood as problems with initiating and maintaining peer relationships (Campbell et al., 2011; Heineman-de Boer, Van Haelst, Cordia-de Haan, & Beemer, 1999).

While there are descriptive data on social functioning in youth with 22q11.2DS, to date, there are no longitudinal 22q11.2DS studies examining childhood predictors of social functioning outcomes in adulthood. A few cross-sectional research studies have examined this research question. In each study, cognitive variables associated with executive functioning or intelligence was identified as being associated with social functioning. In a study conducted by Campbell et al. (2015), 24 adolescents with 22q11.2DS were compared to 27 age-matched typically developing (TD) peers. Parents of the 22q11.2DS group reported significantly more peer relationship problems, as measured by parent-rated peer competence on the Strengths and Difficulties Questionnaire (SDQ; Goodman, Ford, Simmons, Gatward, & Meltzer, 2000). The SDQ is a 25 item questionnaire that uses a 3-point likert scale to measure if the adolescent

displays peer relationship problems, prosocial behavior, emotional problems, conduct problems or hyperactivity/inattention (Goodman et al., 2000). In the 22q11.2DS group, (a) working memory, a subcomponent of executive functioning, which was assessed using a task created for the study, (b) general intelligence, as indexed by the Full scale IQ from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), and (c) emotion attribution, or the ability to understand the emotions of others, measured by the Emotion Attribution Task (EAT; Langdon, Coltheart, & Ward, 2006) were associated with peer relationship problems. These constructs were not related significantly to peer relationship problems in the TD group. The 22q11.2DS group had significantly lower WASI FSIQ scores (M = 75.9, SD = 14.9) than the TD group (M = 108.5, SD = 14.2), performed significantly worse on the working memory measure and made significantly more errors in identifying the facial affect of cartoons (emotion attribution) than the TD group.

Likewise, a cross-sectional study of 100 adults (mean age = 28.8, SD = 9.7) with 22q11.2DS reported social functioning impairments in adults with 22q11.2DS (Butcher et al., 2012). Caregivers or spouse/partner ratings on the Socialization scale of the Vineland Adaptive Behavior Scales (VABS; Sparrow, Balla, & Cicchetti, 1984) were well below average (M = 67.2, SD = 16.9). The mean Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981) or Wechsler Adult Intelligence Scale III (WAIS III; Wechsler, 1997a) full-scale IQ was 71.7 (SD = 9.1) among adults with 22q11.2DS. Butcher et al. (2012) reported a significant positive association between the full-scale IQ and social functioning outcomes. A schizophrenia diagnosis was also a significant predictor of lower VABS socialization scores in this cross-sectional sample. Finally, Butcher et al. (2012) reported non-significant results for congenital heart disease, a lifetime history of a mood/anxiety disorder diagnosis, age, and sex as cross-

sectional predictors of social functioning outcomes in adults with 22q11.2DS. This study is particularly important given that the measurement of social functioning in the current study is derived from the VABS (Sparrow, Cicchetti, & Balla, 2005).

Although cross sectional research in 22q11.2DS is useful for generating hypotheses, it does not permit the field to move forward in developing efficacious interventions designed to prevent/remediate social functioning impairments in this population. Longitudinal studies provide information about potential causal relationships that may be used to inform intervention development. Therefore, it is important to further investigate possible predictors of social functioning outcomes prospectively from childhood to young adulthood in 22q11.2DS (Campbell et al., 2011).

Psychosis and social functioning. Due to the high risk for schizophrenia among individuals with 22q11.2DS, and that the onset of a premorbid period preceding overt psychotic symptoms is typically characterized by social withdrawal and isolation in the general population, further understanding the relationship between psychosis and social functioning in 22q11.2DS is a worthy line of research. Declines in social functioning from childhood to early adolescence are cross-sectionally associated with an increased risk for psychosis in adulthood in 22q11.2DS (Yuen, Chow, Silversides, & Bassett, 2013).

Radoeva, Fremont, Antshel, and Kates (2016) examined the social domain of the Premorbid Adjustment Scale (PAS; Cannon-Spoor, Potkin, & Wyatt, 1982), which assesses social functioning (sociability, withdrawal, and peer relationships) prior to the onset of psychosis, in individuals with 22q11.2DS. When compared to siblings and community controls, individuals with 22q11.2DS experienced more social impairments at all time points (across development from childhood to adulthood). A majority of the 22q11.2DS group experienced

chronically poor or chronically good PAS scores, and only a few individuals had scores that deteriorated across time, demonstrating that the overall (mal)adjustment of individuals with 22q11.2DS was largely consistent across time. However, in this study, the PAS social domain measured in childhood, early adolescence and late adolescence was not a significant predictor of the development of psychosis in adulthood among individuals with 22q11.2DS, indicating that there are other variables that may better predict psychosis in 22q11.2DS. Given that the relationship between psychosis and social impairments in adulthood was not examined, it is possible that concurrent positive symptoms of psychosis in adulthood are more explanatory for social functioning deficits than any childhood variables. In this study, we aim to explore this association.

Childhood Predictors of Adult Social Functioning in Typically Developing Populations

Being that typical and atypical development can be mutually informative in providing useful information about mechanisms of change in social development, it is important to understand what factors have been identified as predictors of social functioning outcomes in typically developing populations. Extremera and Fernández-Berrocal (2006) examined 184 typically developing college students cross-sectionally and found that emotional intelligence or more specifically, emotional attention (the degree to which an individual reports paying attention to his/her feelings [e.g., "I think about my mood constantly"]) was negatively associated and mood repair, or the ability to manage moods (e.g., interrupting negative moods and prolonging positive ones), was positively associated with concurrent self-reported levels of social functioning as measured by the social functioning domain of the 12-Item Short Form Health Survey (SF-12; Ware, Kosinski, & Keller, 1996).

The findings from a longitudinal study of 2076 typically developing individuals assessed in childhood/adolescence (ages 4-16 years) and again 14 years later as adults (ages 18-30 years) suggest that childhood externalizing behaviors are a predictor of poor adult social functioning (Bongers, Koot, van der Ende, & Verhulst, 2008). Bongers et al. (2008) operationalized social functioning as self-report of intimate relationships, daily activities, and spare time activities on the Groningen Questionnaire on Social Behaviour (GQSB; De Jong & Van der Lubbe, 1994). High levels of parent reported childhood oppositional behaviors and status violations on the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) had the strongest associations with adult social functioning impairments (Bongers et al., 2008).

Thus, childhood externalizing behaviors (longitudinally) and the young adult emotional intelligence (cross-sectionally) of typically developing individuals are associated with self-reported social functioning in young adulthood. Please see Table 1 for descriptive information on these studies and other longitudinal studies that predicted adult social functioning from childhood variables. These two studies provide valuable information on factors that predict social functioning in typically developing populations on which to base hypotheses; however, reviewing the existing literature in psychiatric disorders prevalent in, and genetic disorders phenotypically similar to, 22q11.2DS will allow us to potentially identify additional constructs relevant for investigating in 22q11.2DS.

Adult Social Functioning in Psychiatric Disorders Associated with 22q11.2DS

Schizophrenia. Individuals with 22q11.2DS are at high risk for developing schizophrenia (Murphy, 2002) and having a schizophrenia diagnosis is associated with poor social outcomes in adults with 22q11.2DS (Butcher et al., 2012). It is therefore important to understand what underlying factors may be influencing poor social functioning in individuals

with schizophrenia, in order to further examine how these same variables may contribute to social functioning impairments in the 22q11.2DS population.

In comparison to other psychiatric disorders reviewed (see below), social functioning has been more widely investigated in schizophrenia (Burns & Partick, 2007). Both longitudinal and cross-sectional studies have revealed a range of predictors of adult social functioning. Level of education and facial emotion recognition skills were identified as positively associated with social functioning, as measured by the Social Functioning Scale (SFS; Birchwood, Smith, Cochrane, Wetton, & Copestake, 1990) in a cross sectional study of social functioning in 100 adults with schizophrenia (Erol, Ünal, Aydin, & Mete, 2009).

Psychotic symptoms are also associated with social functioning outcomes in longitudinal studies. A study of 49 adult inpatients and outpatients with schizophrenia assessed three times within 18 months found that negative psychotic symptoms were the strongest predictor of social functioning, as measured by the Social Behavior Scale (SBS; Wykes & Sturt, 1986) (Guaiana, Tyson, Roberts, & Mortimer, 2007). Likewise, Lauronen et al. (2007) followed 59 individuals with schizophrenia from birth to age 35 years and found that earlier onset of psychosis and a lack of close friendships in childhood predicted poor social functioning in adulthood, as measured by the Social and Occupational Functioning Assessment Scale (SOFAS; Spitzer, Gibbon, & Endicott, 2000).

Negative symptoms, such as anhedonia, or a lack of social interest, are associated with lower reported social functioning in several cross-sectional studies of adults with schizophrenia (Bora, Eryavuz, Kayahan, Sungu, & Veznedaroglu, 2006; Bowie, Gupta, & Holshausen, 2011; Erol et al., 2009; Rocca et al., 2009). The associations between negative symptoms and social functioning deficits are not surprising as these two constructs share much conceptual overlap;

thus, exploring positive psychosis symptoms (e.g., hallucinations, delusions) and social functioning may be a more effective means of assessing the relationship between schizophrenia and social functioning in 22q11.2DS.

In addition to psychotic symptoms, cognitive deficits have also been reported to be associated with poor social functioning in schizophrenia. For example, processing speed has been found to mediate the relationship between verbal memory and working memory and social functioning, as measured by the social functioning domain of the World Health Organization Disability Assessment Schedule (WHO-DAS; World Health Organization, 1988), in 95 inpatient adults with schizophrenia who were followed prospectively for 6 months (Sánchez et al., 2009). Deficits in executive function, specifically cognitive flexibility as measured by the Wisconsin Card Sorting Test (WCST), were found to be associated with poor social functioning, as measured by the Global Assessment of Functioning (GAF; Jones, Thornicroft, Coffey, & Dunn, 1995), in a cross-sectional study of 168 adult outpatients with schizophrenia (Rocca et al., 2009). Lastly, theory of mind was positively associated with social functioning, as measured by the SFS in a cross-sectional study of 50 outpatients with schizophrenia (Bora et al., 2006). Theory of mind was measured using the Eyes Test, a task in which individuals are shown photographs of only the eyes and are asked to choose a word that describes that person's mental state in the photograph (Bora et al., 2006). The Eyes Test is a commonly used measure of theory of mind that demonstrates good construct validity as described in Vellante et al. (2013).

In contrast, a cross-sectional study of 30 outpatient adults with schizophrenia found no significant associations between social functioning and measures of cognitive functioning such as verbal ability, memory, executive functioning, visual-spatial ability, and attention (Addington, McCleary, & Munroe-Blum, 1998). Addington et al. (1998) used the Social Adjustment Scale-II

(SAS-II; Schooler, Hogarty, & Weissman, 1979) and the Social Dysfunction Index (SDI; Munroe-Blum, Collins, McCleary, & Nuttall, 1996) to measure social functioning. Although these results suggest no significant relations between social functioning and cognitive constructs, the authors noted that their null findings and divergence from other findings may be influenced by the wide variety of instruments used to measure social functioning in the literature. These authors further opined that each instrument may be measuring slightly different constructs, which in turn makes it difficult to compare findings across studies (Addington et al., 1998).

Thus, considering that (a) cognitive variables and psychotic symptoms were associated with social functioning outcomes in individuals with schizophrenia and (b) individuals with 22q11.2DS are at high risk for developing schizophrenia, cognitive variables and psychotic symptoms may also be contributing to poor social functioning outcomes in the 22q11.2DS population and should be further explored.

Attention deficit / hyperactivity disorder (ADHD). Approximately 30-40% of individuals with 22q11.2DS have a comorbid diagnosis of ADHD (Antshel et al., 2006; T. Green et al., 2009). Being one of the most prevalent comorbid psychiatric disorders in 22q11.2DS, identifying the childhood factors associated with poor adult social functioning in individuals with ADHD provides potentially useful information for a better understanding of underlying constructs that may be relevant to social functioning impairments in 22q11.2DS. To our knowledge, few ADHD studies have been conducted that examined this relationship longitudinally.

Similar to the schizophrenia literature, neurocognitive predictors are also associated with social functioning in ADHD. Rinsky and Hinshaw (2011) conducted a 5-year longitudinal study that followed 140 girls with ADHD and 88 matched comparison girls from childhood (ages 6-12)

to adolescence (ages 11-18). Results indicated that childhood executive function abilities, specifically planning and response inhibition, predicted adolescent social functioning. These findings suggest that the inability to inhibit one's behaviors while interacting with peers might negatively affect one's level of social functioning. In this study, a multi-informant, multi-measure omnibus composite of social functioning was created by summing the standard scores of the Dishion Social Preference Scale (DSPS; Dishion & Kavanagh, 2003), the Social Skills Rating System (SSRS; Gresham & Elliot, 1990), the Social Relationships Questionnaire (SRQ; Buhrmester & Furman, 1990), the CBCL Social Competence Scale, and the Teacher Report Form (TRF; Achenbach, 1991) Social Competence Scale (Rinsky & Hinshaw, 2011).

Likewise, Diamantopoulou, Rydell, Thorell, and Bohlin (2007) found that a composite score of executive function deficits (including response inhibition and working memory) and high levels of ADHD symptoms in 112 children (62 girls, 50 boys; mean age = 8) were both associated negatively with peer acceptance one year later. The authors utilized a peer nominations questionnaire completed by classmates that specifically assessed social preference, physical aggression, relational aggression, and prosocial behavior in classmates.

In contrast to these significant findings, there is research to suggest there is no relationship between cognitive constructs and social functioning in ADHD. Øie, Sundet, and Ueland (2011) found no significant cognitive predictors of social functioning in young adults with ADHD. The authors assessed executive function, visual memory, verbal memory, visuomotor processing, motor coordination, auditory attention, selective attention, and visual attention in a 12-year longitudinal study that followed 19 individuals with ADHD from adolescence (ages 12-18) to young adulthood (ages 24-30). The authors used the SFS, the Adult Self Report scale (ASR; Achenbach & Rescorla, 2003), and the Global Assessment Scale of

Function (GAS; Endicott, Spitzer, Fleiss, & Cohen, 1976) to assess social functioning (Øie et al., 2011). Biederman et al. (2004) also found no significant associations between executive function and social functioning, as measured by the Social Adjustment Inventory for Children and Adolescents (SAICA; Orvaschel & Walsh, 1984), in a cross sectional study of 259 children and adolescents with ADHD (ages 6-17 years). Thus, the conflicting findings of these studies suggest that the relationship between cognitive factors and social functioning in individuals with ADHD is complex and varies likely as a function of the study design and measures employed. Further research is needed to understand these likely dynamic relationships.

Anxiety disorders. In addition to ADHD, anxiety disorders are also prevalent in 22q11.2DS with nearly 50% of individuals with 22q11.2DS also having an anxiety disorder diagnosis (Green et al., 2009). Although no longitudinal studies examining childhood predictors of adult social functioning in individuals with anxiety disorders were identified, several cross-sectional studies provide relevant information. A cross-sectional study of 161 children and adolescents (ages 7 to 14) with Generalized Anxiety Disorder, Social Phobia, and/or Separation Anxiety Disorder found that increased severity of the child's anxiety disorder, as measured by the Anxiety Disorder Interview Schedule for DSM-IV: Child and Parent Version (ADIS-C/P; Silverman & Albano, 1996), was related to poor social functioning, as measured by the CBCL and the TRF (Settipani & Kendall, 2013). This suggests that high levels of anxiety may impair one's ability to make and keep friends and/or that social impairments may create anxiety.

Positive affect and emotion regulation were associated with higher social functioning, as measured by the Asher Loneliness Scale (ALS; Asher, Hymel, & Renshaw, 1984), the Social Experience Questionnaire (SEQ; Crick & Grotpeter, 1996), the CBCL, and the TRF, in a cross-sectional study of 90 children (ages 6-12 years) with a diagnosis of Generalized Anxiety

Disorder, Social Phobia, and/or Separation Anxiety Disorder (Jacob, Suveg, & Whitehead, 2014). Since only cross-sectional studies exist presently, further research should be conducted to prospectively examine these factors and others that may be related to social functioning. Prospective studies will enable more focused childhood prevention intervention efforts to be developed and initiated in children as a way of improving adolescent and adult social functioning.

Autism spectrum disorder (ASD). General social impairments are associated with an ASD diagnosis, making childhood factors that prospectively predict social outcomes in adulthood a widely researched topic in this population. Gillespie-Lynch et al. (2012) conducted a longitudinal study of 20 individuals with ASD evaluated in early childhood (mean age = 3.9 years, SD = 1.2), adolescence (mean age = 11.7 years, SD = 3.2), young adulthood (mean age = 18.3 years, SD = 3.6) and adulthood (mean age = 26.6 years, SD = 3.8) and found that responsiveness to joint attention and language skills in childhood predicted social functioning in adulthood, as measured by a composite score based on employment, living situation, and friendships.

Early reciprocal interaction impairments predicted poor adult social functioning as measured by the Family History Schedule (FHS; Bolton et al., 1994) in a study of 60 individuals with ASD assessed in childhood (mean age = 6.9 years, SD = 2.9) and again as adults (mean age = 44.2 years, SD = 9.4) (Howlin, Moss, Savage, & Rutter, 2013). This finding suggests stability of social functioning across time in ASD. In addition, childhood nonverbal IQ was only significant after controlling for overall level of language and early symptoms of ASD as measured by the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003) (Howlin et al., 2013). This implies that language development in childhood may be more

closely related to an individual's ability to make and maintain friendships/relationships later in life. Considering individuals with 22q11.2DS also experience delayed language abilities in childhood, this is a useful construct to further investigate in the 22q11.2DS population.

A direct observation study compared 63 high functioning children with ASD (mean age = 8.3) to a group of 33 children diagnosed with a variety of developmental language disorders (mean age = 8.5) (Manning & Wainwright, 2010). The children's level of play was coded by the frequency of social behaviors and overall quality of social behavior in two 3-minute videotaped segments of a play session (Manning & Wainwright, 2010). A significant positive association between high level play (e.g., pretend play and rule based play) and social functioning was reported in both groups (Manning & Wainwright, 2010). This suggests that a lack of high level play with others, typically seen in individuals with ASD, may have a negative impact on their social functioning. This finding (association between high level play and social functioning was significant in both groups) also suggests that this relationship is not specific to ASD.

Lastly, parent report of impairment in executive function as measured by the global executive composite score of the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) was negatively associated with social functioning as measured by the Socialization scale of the VABS in a cross-sectional study of 35 children and adolescents (30 boys and 5 girls) with ASD (M = 10.5 years old; SD = 3.0) (Gilotty, Kenworthy, Sirian, Black, & Wagner, 2002). The findings of this study are particularly relevant given that the current study uses the VABS to operationally measure social functioning. Thus, as noted in Table 1, many longitudinal factors have been identified among individuals with ASD as relevant constructs to examine in relation to social functioning outcomes in adulthood. Considering the

elevated prevalence rates of comorbid ASD diagnosis among individuals with 22q11.2DS, these same constructs merit exploration prospectively.

Adult Social Functioning in Genetic Disorders that are Phenotypically Similar to 22q11.2DS

Of the genetic disorders reviewed, to our knowledge, there is only one longitudinal study that identified factors associated with social functioning outcomes. In a longitudinal study with individuals with Fragile X Syndrome (FXS), Chromik et al. (2015) evaluated 73 individuals with FXS in late childhood (Mean age = 12.3 years, SD = 2.7) and again in late adolescence/young adulthood (Mean age = 20.4 years, SD = 2.9). Higher symptoms of hyperactivity in childhood were significantly predictive of social functioning impairments later in life, as measured by the Socialization scale of the VABS and the Social Problems Scale of the CBCL. Consistent with previously reviewed ADHD literature (Diamantopoulou et al., 2007), children who exhibit more symptoms of hyperactivity may have more difficulty attending and responding appropriately in social situations. These findings are particularly relevant because the VABS is also used to measure social functioning in the current study.

In addition to this one longitudinal study, cross-sectional studies of individuals with Turner syndrome, Down syndrome, and Fragile X syndrome have been published; however, no studies were found for Klinefelter syndrome, Prader-Willi syndrome, Williams syndrome or other microdeletion syndromes. Among the genetic disorders reviewed, neurocognitive impairments were the most common factors associated with social functioning. A study of 40 girls with Turner syndrome and 19 typically developing children, all between ages 5 and 12, found that parent report of global executive function, measured using the BRIEF, explained the largest amount of variance in the Social Responsiveness Scale (SRS; Constantino & Gruber,

2005), a measure of social functioning (Lepage, Dunkin, Hong, & Reiss, 2013). In another study, working memory, inhibitory control, and nonverbal IQ were positively related to parent reported measures of social functioning, as measured by the Harter Self-Perception Profile for Adolescents (SPPA; Harter, 1988) and the Socialization scale of the VABS, in a study of 20 girls with FXS (mean age = 14.91 years) and 20 age-matched typically developing peers (Turkstra, Abbeduto, & Meulenbroek, 2014). The cognitive variables associated with social functioning in Turkstra et al. (2014) are particularly important because the VABS Socialization scale was used to measure social functioning, which is also the instrument used in the current study to operationally measure this construct.

There were only two studies that examined constructs other than neurocognitive impairments as possibly being related to social functioning problems. Dressler, Perelli, Bozza, and Bargagna (2011) investigated ASD in Down syndrome and included 24 participants (mean age= 21.9, SD= 6.4): 8 individuals with Down syndrome and ASD, 8 individuals with Down syndrome alone, and 8 individuals with ASD alone. Results indicated that a comorbid diagnosis of ASD in individuals with Down syndrome was associated with poorer social functioning, as measured by the VABS Socialization scale, when compared to groups of individuals with Down syndrome or ASD alone. These findings are particularly relevant because the VABS Socialization scale was also used to measure social functioning in the current study.

No significant associations were found in a study that examined the relationship between physical appearance and social functioning in 111 children (ages 6 to 14) with Down syndrome (Cunningham, Turner, Sloper, & Knussen, 1991). The authors used an appearance scale that was completed by teachers to assess height, weight, facial appearance, general appearance, and physical attractiveness (Cunningham et al., 1991).

Conclusions

Identified constructs. Considering that no previous research has considered childhood predictors of adult social functioning outcomes in 22q11.2DS, identifying constructs associated with social functioning difficulties in disorders prevalent among individuals with 22q11.2DS is important for hypothesis generation. Using variables identified in previous cross-sectional studies in 22q11.2DS and variables most frequently identified across the genetic and psychiatric disorders reviewed, our study aims to further investigate the prospective relationships between these variables and social functioning in the 22q11.2DS population.

As seen in Table 1, the few studies that have longitudinally examined childhood predictors of adult social functioning indicate that externalizing behaviors, a lack of close childhood friends, early onset of psychiatric symptoms, weak executive functions, poor responsiveness to joint attention, limited reciprocal interaction, and weak language skills may be possible childhood factors to explore as predictors of adult social functioning in 22q11.2DS.

When considering both cross-sectional and longitudinal studies, as seen in the summary presented in Table 2, executive function impairments were the most frequently identified factor associated with poor social functioning across psychiatric and genetic disorders associated with / phenotypically similar to 22q11.2DS. More specifically, executive dysfunction was identified as a longitudinal predictor of social functioning in both schizophrenia and ADHD, as well as having a correlational relationship with social functioning in ASD, Turner syndrome, and Fragile X syndrome. In addition, working memory, a subcomponent of executive functioning, was associated cross sectionally with social functioning in 22q11.2DS. All of the above provides converging evidence to support that poor executive functioning is related to impaired social functioning in various disorders and shows the need for further investigation of this cognitive

construct longitudinally. Our study will prospectively examine various executive function subcomponents to investigate the longitudinal relationship between specific childhood executive functions and young adult social functioning outcomes. By studying individual executive functioning domains separately, we aim to provide more specific clinically relevant information that may be useful for developing interventions in childhood towards reducing the social functioning impairments in adulthood.

Factors related to social cognition, including emotional intelligence, emotion recognition, and emotion regulation, were also commonly identified as being associated with social functioning in cross-sectional studies of typically developing individuals, individuals with schizophrenia, and individuals with anxiety disorders. Likewise, emotion attribution, or the ability to understand the emotions of others, was associated with social functioning in 22q11.2DS. Therefore, to further investigate this relationship and longitudinally examine how emotion relates to social functioning outcomes, an aspect of social cognition (emotion recognition) will also be assessed in our study.

In addition, since social skills are a highly related construct to social functioning (Halford & Hayes, 1995), are commonly the first line of intervention to remediate social functioning problems, and were predictive of social functioning impairments in the ASD literature, we will further investigate this relationship longitudinally in individuals with 22q11.2DS. Finally, given that our study aims to inform prevention/remediation efforts for poor social functioning in the 22q11.2DS population, it is also important to consider factors specific to 22q11.2DS that were not identified or less commonly identified in the studies previously reviewed (e.g., internalizing symptoms, Full-scale IQ) as possibly predictive of social functioning outcomes in 22q11.2DS.

Methodological constraints. As seen in Table 1, a rather wide and varied number of

measures have been used to assess social functioning, a construct that has been defined in many different ways. This makes it difficult to compare results across studies. It is possible that while all labeled social functioning, the constructs being assessed actually differ between studies. For instance, some instruments may be measuring both social skills and social functioning and others are including items related to occupational functioning. For this reason, we have selected measures that assess social interactional functioning and not other constructs. Likewise, the respondent (e.g., parent, teacher, peers, self-report) varied across instruments and between studies making it difficult to compare results. Considering that most previous studies rarely included both self and collateral reports, both a self-report and parent-report measure will be used in our study.

Clinical significance. Identifying childhood variables that prospectively predict social functioning in adulthood can provide clinically useful information for the 22q11.2DS population. Given the high rate of schizophrenia in the 22q11.2DS population and the data suggesting that a lack of childhood social relationships are predictive of schizophrenia in the non-22q11.2DS population (Lauronen et al., 2007), it is possible that prevention efforts could be potentially developed and tested in the 22q11.2DS population based upon any identified childhood predictors. In addition, since social abilities are related to quality of life (Tobin, Drager, & Richardson, 2014), identifying factors related to adult social functioning in 22q11.2DS may provide insight into guiding efforts to improve quality of life.

Specific Aims / Hypotheses

This project investigates a clinically significant and novel research topic that has clear implications for intervention development and potentially prevention. We included both siblings and community controls as comparison groups to (a) examine differences in social development,

(b) control for environmental effects shared by siblings, and (c) investigate if predictors in the 22q11.2DS group are specific to the population, as indicated by between group differences in childhood factors predicting social functioning. The four specific aims and associated hypotheses of the present study are:

Specific aim 1: **Describe social functioning outcomes in young adults with 22q11.2DS compared to siblings and community controls using both self- and parent-report measures.** We hypothesize that young adults with 22q11.2DS will have lower self- and parent-reported social functioning when compared to both siblings and community controls.

Specific aim 2. **Examine the relationship between concurrent positive symptoms of psychosis and social functioning in 22q11.2DS**. Based upon a previous 22q11.2DS study (Butcher et al., 2012), we hypothesize that there will be a negative correlation between social functioning and positive symptoms of psychosis in young adulthood in 22q11.2DS. Given the very limited number of siblings and community controls expected to have positive symptoms of psychosis, this specific aim will only be considered in the 22q11.2DS group.

Specific aim 3: **Identify potential childhood cognitive predictors of young adult social functioning in all three groups (22q11.2DS, siblings, community controls).** Full scale IQ was previously noted to be associated with social outcomes in 22q11.2DS cross-sectional studies (Butcher et al., 2012; Campbell et al., 2015). The most consistent finding in the literature reviewed above is the centrality of executive functioning to social functioning impairments. Based upon both of these literatures, we hypothesize that childhood Full Scale IQ (Specific Aim 3a) will significantly predict young adult social functioning in 22q11.2DS and executive functioning (Specific Aim 3b) will significantly predict young adult social functioning in all 3 groups.

Specific aim 4: **Identify potential childhood behavioral / emotional predictors of young adult social functioning in all three groups (22q11.2DS, siblings, community controls).** Factors related to social cognition, including emotion recognition, were commonly associated with social functioning in the literature reviewed in typically developing populations and psychiatric/genetic disorders common in 22q11.2DS; therefore, we hypothesize that emotion recognition will significantly predict young adult social functioning in all three groups. In addition, as evidenced by the findings of studies investigating disorders comorbid with 22q11.2DS, we hypothesize childhood externalizing behaviors will significantly predict young adult social functioning in all three groups. The findings of Shashi et al. (2012) suggest that internalizing behaviors are associated with social functioning problems in 22q11.2DS; therefore, we also hypothesize that childhood internalizing behaviors will significantly predict young adult social functioning in the 22q11.2DS group. Lastly, since displaying poor social skills, such as joint attention problems and reciprocal interactions impairments, were identified as predictive of social functioning impairments in ASD (Gillespie-Lynch et al., 2012; Howlin et al., 2013), we hypothesize that child social skills will significantly predict young adult social functioning in all three groups.

Exploratory aim 1. For any significant findings in Specific Aim 3 or 4, we will explore adolescent family environment and parent/child characteristics contributing to parental stress (time 2) as mediators of the relationship between any significant childhood cognitive / behavioral / emotional variables (time 1) and young adult social functioning (time 4). Our exploratory aim will only be considered if significant childhood cognitive/behavioral/emotional predictors emerge in Specific Aim 3 or 4 for the 22q11.2DS group.

Parent/child characteristics contributing to parental stress was chosen as a potential

mediator based on previous literature suggesting that parents/primary caregivers of children/adolescents with 22q11.2DS report three times higher stress levels compared to parents of typically developing children (Briegel, Schneider, & Schwab, 2008). In addition, non-22q11.2DS research suggests that stress experienced by parents is significantly associated with the frequency of problem behaviors displayed by children (Plant & Sanders, 2007) and approximately 60% of children with 22q11.2DS have clinically significant behavior problems (Briegel et al., 2008). Since parental stress negatively predicted the quality of peer-based social interactions in children with developmental delays (Guralnick, Hammond, Connor, & Neville, 2006), it is possible that a similar pattern will emerge in 22q11.2DS, such that parental stress may influence parent-child interactions (e.g., negative responses from parents), contributing to poor social functioning outcomes. Therefore, we were interested in testing the hypothesis that parent/child characteristics contributing to parental stress (e.g., adolescent problem behaviors, parental health, etc.) would mediate the relationship between childhood cognitive/behavioral/emotional variables and social functioning outcomes in adulthood.

Family environment was also chosen as a potential mediator because parents of children with 22q11.2DS report experiencing marital conflict and having lower than average expectancies for their children for functional independence and academic achievement, thereby requiring more close supervision (Allen et al., 2014; Prinzie et al., 2004). Since family environment can influence social functioning (e.g., modeling how to resolve conflicts) in typically developing adolescents (Youngblade et al., 2007), we were interested in testing the hypothesis that the family environment of families with an adolescent with 22q11.2DS would also mediate the relationship between childhood cognitive/behavioral/emotional factors and adulthood social functioning.

Method

Participants

Recruitment. This 9-year longitudinal study consisted of individuals with 22q11.2DS, their siblings, and community control participants who were each assessed at four time points. Participants with a fluorescence in situ hybridization-confirmed deletion of 22q11.2 and their age and gender matched siblings were recruited through local advertisements and from the Center for the Diagnosis, Treatment, and Study of 22q11.2DS at SUNY-Upstate Medical University. Sibling control participants were included in this study to account for possible environment-specific variables (e.g., socioeconomic status, home environment, etc.) that may influence social functioning within the family. Group age and gender matched community control participants were recruited from local public schools via advertisements. Neither group of control participants received formal molecular genetic screening, as 22q11.2DS is readily identifiable by a facial phenotype. In all three groups, children with an identifiable genetic disorder (other than 22q11.2DS) or children with an identifiable neurological condition (e.g., traumatic brain injury, pre-term birth) that is known to affect cognitive or psychiatric function were excluded from participation. Given the developmental delays that are associated with 22q11.2DS, no attempt was made to exclude community control participants with ADHD and learning disabilities (LD). Children in the community control group were excluded if they were not taught in a general education classroom.

Demographics. Participants in this study were part of a longitudinal study beginning in childhood and were assessed four times (every three years). Participation in the study spanned a total of 9 years. For the current project, only participants who completed the parent-report outcome measure of social functioning at Time 4 and who also had Time 1 data were included in

this study to examine relationships prospectively. Our sample consisted of 53 children with 22q11.2DS, an age and gender matched group of 18 siblings of children with 22q11.2DS and 16 community controls (CC).

At Time 1, the average age of individuals with 22q11.2DS was 11.9 years (SD = 2.1), 12.5 years for siblings (SD = 2.0), and 11.2 years for CC (SD = 1.6). At Time 4, the average age of 22q11.2DS participants was 21.3 years (SD = 2.2), siblings on average were 21.9 years (SD = 1.8), and CCs were 20.4 years (SD = 1.5). The 22q11.2DS, sibling, and CC groups did not differ significantly on age at Time 1, F (2, 84) = 1.80, p = .172, age at Time 4 F (2, 84) = 2.22, p = .115, gender distribution X^2 (2, N = 87) = 1.51, p = .471, race, X^2 (2, N = 86) = 5.95, p = .203, or ethnicity, X^2 (2, N = 87) = .828, p = .661. Please see Table 3 for complete demographic information.

Attrition. Given that we imposed strict participation criteria (had to have both Time 1 and Time 4 data), not all participants in the larger study are included in our analyses. Thus, we consider how our sample compares to the larger study sample.

When comparing our study sample to all individuals who participated at Time 1, we found no differences in attrition between the three groups X^2 (2, N = 129) = .670, p = .715. Furthermore, participants lost at follow up sometime between Time 1 and Time 4 did not differ from those who followed-up on any relevant Time 1 socio-demographic measures including participant age F (1, 127) = .001, p = .974, gender X^2 (1, N = 87) = .089, p = .766, and socioeconomic status F (1, 109) = 2.95, p = .089. Likewise, participants lost to follow up did not differ from those who did follow up on any relevant social and cognitive measures, including Time 1 Vineland Socialization scores F (1, 122) = .019, p = .890, Time 1 FSIQ F (1, 127) = .549, p = .460, and Time 1Verbal IQ F (1, 127) = .742, p = .391. Thus, the participants who have

both Time 1 and Time 4 data appear to be representative of the larger Time 1 sample.

Psychiatric Measure

Given the longitudinal nature of this study, Table 4 presents the timeline of when our measures were administered. Participants were assessed at four different time points; however, information from time 3 is not used in the current study due to not being relevant to the specific aims of our project.

Structured Interview for Prodromal Symptoms (SIPS) (Miller et al., 2003). The Structured Interview for Prodromal Symptoms (SIPS) is a commonly used structured interview that evaluates current symptoms and clinical risk of psychosis. Previous research indicates that the SIPS has good predictive value of correctly identifying 67% of individuals who later developed psychosis at a 24 month follow up (Miller et al., 2003). In the current study, the full SIPS was administered to participants in young adulthood (Time 4), yet due to the conceptual overlap between negative symptoms and social functioning, only the Positive Symptom domain score was used in analyses. The Positive Symptom domain includes questions related to the presence of positive psychotic symptoms, such as unusual thought content, suspiciousness, ideas of grandiosity or persecution with delusional features, hallucinations, or disorganized speech. Higher scores on the SIPS indicate the presence of more positive symptoms of psychosis.

Young Adult Outcome Measures

Social Adjustment Scale - Self-Report (Weissman, 1999). The Social Adjustment Scale - Self-Report (SAS-SR) is a 54-item self-report scale that measures social adjustment over the past two weeks. The measure is intended for individual's ages 17 years and older. The SAS-SR identifies six social role areas, including work, social and leisure activities, relationships with extended family, role as a spouse or partner, parental role, and role within the family unit. An

area is not assessed if the respondent indicates that the questions are not relevant to them (i.e., if the respondent does not have children or is not married). Each item is rated on a five-point Likert scale. Summing the item responses and dividing by the total number of items answered in that section calculates mean scores for each of the six role areas. These mean scores are then transformed into *T*-scores (M= 50, SD= 10) based on a normative sample, with higher scores indicating more social impairment.

For the present study, the standard score of Social and Leisure Domain was used as a self-report measure of social functioning. The SAS-SR Social and Leisure Domain includes questions such as, "how many friends have you been in contact with in the last 2 weeks" and "how many times in the last 2 weeks have you gone out socially with other people." As previously noted, we operationalize social functioning as an individual's ability to make, maintain, and be satisfied with his/her social relationships. We only used the Social and Leisure Domain of the SAS-SR to assess this construct because all other domains assess social adjustment within microsystems related to social roles (e.g., within the workplace and family unit). We examined differences between our three groups (22q11.2DS, siblings and community controls) across all of the SAS-SR domains to provide descriptive information about the social adjustment of individuals with 22q11.2DS when compared to same aged peers. However, the Social and Leisure Activities domain score was used as our outcome variable because we were interested in examining the quality of social functioning mainly regarding social relationships and social activities.

The normative sample used to standardize the SAS-SR consisted of 482 community respondents (*N* = 205 males and 277 females) ranging from 24 to 70 years old (Weissman, Prusoff, Thompson, Harding, & Myers, 1978). Information was also collected from a clinical

population of outpatients with depression (*N* = 191), substance use problems (*N* = 54) and schizophrenia (*N* = 47). These populations were nationally representative of gender, age, race/ethnicity, income, and geographical region (Weissman et al., 1978).

The SAS-SR has acceptable internal consistency (mean α coefficient = .74) and test-retest reliability over a two week period (mean α coefficient = .78) (Edwards, Yarvis, Mueller, Zingale, & Wagman, 1978). Convergent validity between the SAS-SR and the 36-Item Short-Form Health Survey (Ware, Snow, Kosinski, & Gandek, 1993), Social Adaptation Self-Evaluation Scale (Bosc, Dubini, & Polin, 1997) was demonstrated by Weissman, Olfson, Gameroff, Feder, and Fuentes (2001). The Social and Leisure Domain of the SAS-SR was significantly correlated ($r = 0.47$, $p < .0001$) with questions related to social functioning on the 36-Item Short-Form Health Survey and significantly correlated ($r = 0.63$, $p < .0001$) with the total score of the Social Adaptation Self-Evaluation Scale, which is used to assess social motivation.

Vineland Adaptive Behavior Scales, Second Edition (Sparrow et al., 2005). The Vineland Adaptive Behavior Scales- 2nd edition (VABS-II) is the most widely administered clinical instrument used to assess adaptive behavior. Several administration options include; a semi-structured survey interview, parent/caregiver checklist rating form, and teacher checklist rating form. Respondents are asked to rate their own or the participant's ability to independently perform behaviors across three domains: Communication (receptive, expressive, written skills), Daily Living Skills (personal, domestic, community-related skills), and Socialization (interpersonal relationships, play and leisure, coping skills). The VABS-II Parent/Caregiver Rating Form was used in the current study and is a 297-item questionnaire rated on a 3-point scale: 2 (usually), 1 (sometimes or partially), 0 (never). Standard scores (M= 100, SD= 15) are provided for each domain, with higher scores indicating better functioning. For the present study,

only the standard score of the Socialization scale was used as a parent-report of social functioning.

To standardize the VABS-II, a sample of 3,695 individuals ages birth to 90 were assessed at 242 sites in 44 states of the United States. The standardization sample was nationally representative of race, ethnicity, and socioeconomic status. The internal consistency reliability estimates of the subdomains are in the moderate to high range (0.75 or greater). The VABS-II has high split half, inter-rater (Sparrow et al., 1984), and test-retest reliability coefficients for each domain, with most being in the upper .80's to low .90's range (Sparrow et al., 2005).

Childhood Cognitive Predictors

Wechsler Intelligence Scale for Children- 3rd edition (Wechsler, 1991). The Wechsler Intelligence Scale for Children-3rd edition (WISC-III) is a standardized test that measures an individual's level of intellectual functioning and several other related neuropsychological constructs. The WISC-III contains ten required subtests from which three composite scores are calculated: Verbal IQ (VIQ), Performance IQ (PIQ), and Full Scale IQ (FSIQ). The subtests used for the VIQ are: Arithmetic, Comprehension, Information, Similarities, and Vocabulary. The subtests that make up the PIQ are: Block Design, Coding, Object Assembly, Picture Arrangement, and Picture Completion. All ten subtests are used to calculate the composite score FSIQ, with a mean of 100 and a standard deviation of 15. Four index scores are also provided that represent more narrow areas of cognitive function, including the Verbal Comprehension Index (VCI), the Perceptual Organization Index (POI), the Freedom from Distractibility Index (FDI), and the Processing Speed Index (PSI). For the present study, FSIQ and Verbal IQ were used to assess general intellectual functioning and language abilities respectively, and the Freedom from Distractibility index score (composite of Arithmetic and

Digit Span subtests) was used to examine working memory. Construct validity for the Freedom from Distractibility as a measure of both working memory and attention has been adequately demonstrated in various studies (Wechsler, 1991). Mayes and Calhoun (2006) compared the WISC-III FDI to the WISC-IV Working Memory Index (WMI) and found small differences (*d* = 0.1), indicating that the FDI is measuring a similar construct as the WMI an adequate measure of working memory. Concurrent validity is also provided for the WISC-III as a measure of general intelligence when compared to other tests designed to measure general intelligence (e.g., Differential ability Scales (Elliot, 1990) and Stanford-Binet Intelligence Scale, Fourth Edition (Thorndike, Hagen, & Sattler, 1986)), with FSIQ correlations ranging from .65 to .96 and Verbal IQ .75 to .96. (Wechsler, 1991). The WISC-III is a widely used instrument with evidence to support good reliability (Kaplan & Saccuzzo, 2001).

Gordon Diagnostic System (Gordon, McClure, & Aylward, 1989). The Gordon Diagnostic System (GDS) is a continuous performance test (CPT) that objectively measures sustained attention and response inhibition, the latter a subdomain of executive functioning. The GDS was the first continuous performance test created and has been extensively used with individuals with ADHD. Studies have shown significant agreement between the GDS subtest scores and other behavior rating scales and behavioral instruments measuring attention and response inhibition (Fischer, Barkley, Fletcher, & Smallish, 1993; McClure, McClure, Gordon, & Gordon, 1984). The vigilance task of the GDS assesses an individual's self-control during a task that requires sustained attention. During this task, the participant is asked to press a blue button when a "9" follows a "1" on the computer screen. The GDS provides scores for errors of omission and commission that can be transformed into standardized Z-scores based upon age norms. Errors of omission (i.e., missing a target when it is presented) is considered a measure of

inattention, whereas commission errors (i.e., pushing the button in response to anything other than the target) are commonly used as a measure of impulsive behaviors (poor response inhibition) (Gordon et al., 1989). For the present study, only the standardized commission errors score were used in the analyses. Lower z-scores are indicative of poorer response inhibition and making more errors of commission. The GDS is a commonly used behavioral measure of attention and response inhibition that demonstrates good psychometric properties (Gordon & Mettelman, 1988).

Tower of London (Shallice, 1982). The Tower of London (TOL) is commonly used to measure aspects of executive function. Spatial problem-solving, planning, response inhibition, and working memory are all required to successfully complete the TOL task (Berg & Byrd, 2002). However, the TOL is generally considered a measure of planning and has demonstrated good construct validity as a measure of planning (Culbertson & Zillmer, 1998). The TOL includes three pegs of different lengths and three colored balls. The objective of this task is to rearrange the balls into a specific configuration using the fewest moves possible. The large, medium, and small sized pegs can only hold 3 balls, 2 balls, or 1 ball. Participants can only move one ball at a time. Total number of moves is calculated, with fewer moves indicating better planning skills. For the present study, total number of moves was used to assess planning abilities. Adequate concurrent validity for the TOL as a measure of planning was demonstrated in Sullivan, Riccio, and Castillo (2009). Empirical evidence for satisfactory reliability has been demonstrated for the TOL task (Humes, Welsh, Retzlaff, & Cookson, 1997).

Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993). The Wisconsin Card Sorting Test (WCST) is a task that measures cognitive flexibility, a subdomain of executive functioning. In this task, participants are asked to match a stimulus card to one of

the four cards presented above. The participant is immediately given verbal feedback from the examiner indicating if their choice was "correct" or "incorrect." The test is complete if all six categories are successfully finished or if all 128 cards are used. Standard scores for perseverative errors (i.e., after receiving feedback that the incorrect sorting feature was used, the participant continues to sort the cards based on that incorrect feature) and non-perseverative errors are calculated. For the present study, scores for perseverative errors and non-perseverative errors were used to assess cognitive flexibility. Higher standard scores are indicative of better cognitive flexibility. The Wisconsin Card Sorting Test has been considered a valid measure of executive functioning (Heaton et al., 1993) and demonstrates good test-retest reliability and high inter-rater reliability (Axelrod, Goldman, & Woodward, 1992). Factor analytic studies suggest that the WCST is a valid measure of the construct cognitive flexibility (Goldman et al., 1996; Greve, Ingram, & Bianchini, 1998; Greve, Stickle, Love, Bianchini, & Stanford, 2005).

Stroop Color-Word Test (Golden, 1978). The Stroop Color-Word Test is a task that measures cognitive flexibility, selective attention and response inhibition. There are three trials on the Stroop test. During the word task, participants are asked to name the word. Next, participants are asked to state the colors of the XXX's. Last, the color words (e.g. "yellow") are presented in different colored font, and participants are asked to name the color of the ink that the words are written in. Participants are instructed to read as many stimuli as they can in 45 seconds. Standardized T-scores are provided for color, word, color-word and interference trials. The interference T-score was used in the present study, with lower T-scores on the interference trial indicating weaker cognitive flexibility and poorer response inhibition. The Stroop Color-Word Test demonstrates good psychometric properties, as evidenced by moderate/high internal consistency and stable test-retest reliability (Franzen, Tishelman, Sharp, & Friedman, 1987).

Good construct validity has been demonstrated in several studies indicating that the Stroop Color-Word Test is a valid measure of both response inhibition and cognitive flexibility, (Boone, Miller, Lesser, Hill, & D'Elia, 1990; Homack & Riccio, 2004; Strauss, Sherman, & Spreen, 2006).

California Verbal Learning Test-Children's version (Delis, Kramer, Kaplan, & Ober, 1994). The California Verbal Learning Test-Children's Version (CVLT-C) measures auditory/verbal learning and working memory. During the CVLT-C, a list of 15 words belonging to three semantic categories is provided to the participant. The participant is asked to recall the words. Scores are provided for list learning, interference trial, and levels of immediate and delayed recall. In the present study, scores for List A Trial 1 (recall after hearing the list once), List A Trial 5 (recall after hearing the list five times), and List B (interference) were used to assess working memory. The CVLT-C was normed using 920 children ages 5 through 16 years randomly sampled from the U.S. Census. The sample was equally representative of age, gender, race/ethnicity, geographic region and parent education level. The CVLT-C is a widely used measure in research that demonstrates good internal consistency and sufficient test-retest reliability (Delis et al., 1994). The CVLT-C is moderately correlated with the Children's Memory Scale, a measure that also examines learning and memory, including both working and long-term memory, in children, indicting good convergent validity for the CVLT-C as a measure of working memory (Cohen, 1997; Strauss et al., 2006).

Visual Span Test (Davis, 1998). The Visual Span Test is a computer-based test that assesses visual working memory abilities. It was adapted from the Visual Memory Span subtest of the Wechsler Memory Scale – Third Edition (Wechsler, 1997b). During the Visual Span Test, an array of squares is presented randomly on the screen. For each trial, a number of the squares

are illuminated in a particular order and the participant must reproduce the sequence. The sequences increase in length, making it more difficult to reproduce the pattern. The forward and backward span standardized z-scores were used to assess working memory. The Visual Span Test is a well-validated instrument with good construct validity as a measure of working memory (Wechsler, 1997b) and demonstrates good reliability (Franzen, 2013).

Childhood Emotional / Behavioral Predictors

Penn Emotion Recognition- 40 Test (Gur et al., 2001). The Penn Emotion Recognition-40 Test (Penn ER- 40) is a computerized test that assesses the ability to identify facial expressions of emotion. Participants are presented with 40 color photographs of adult faces and are asked to rate each on a 7-point Likert scale from "very unhappy" to "very happy." The stimuli are balanced by gender and ethnicity with 21 white and 19 non-white faces (Weiss et al., 2007). Correct responses receive a score of 1 and incorrect responses 0, with higher scores indicating better facial emotion recognition. For the present study, responses were scored as correct if it was correct or within one point of the correct answer. The Penn ER-40 demonstrates good test-retest reliability (Weiss et al., 2007) and adequate construct validity when correlated with other measures of social cognition (Pinkham, Penn, Green, & Harvey, 2016).

Behavior Assessment System for Children - Parent Rating Scale (Reynolds & Kamphaus, 1992). The Behavior Assessment System for Children- Parent Rating Scale (BASC-PRS) is a measure of parent-reported behaviors of children and adolescents. The BASC-PRS has versions for preschool aged children from 2-5 years, children ages 6-11 years, and adolescents ages 12-21 years. All items are rated on a 4-point frequency scale, ranging from "Never" to "Almost always." Responses are organized into nine clinical scales (i.e. Aggression, Anxiety, Attention Problems, Atypicality, Conduct Problems, Depression, Hyperactivity, Somatization,

and Withdrawal), five adaptive behavior scales (i.e. Adaptability, Activities of Daily Living, Functional Communication, Leadership, and Social Skills), and seven content scales (i.e. Anger Control, Bullying, Developmental Social Disorders, Emotional Self-Control, Executive Functioning, Negative Emotionality, and Resiliency). Item raw scores are transformed into T-scores (M= 50, SD= 10), with higher scores on the clinical scales and content scales indicating more maladaptive behaviors, and higher scores on the adaptive behavior scales indicating a higher frequency of adaptive behaviors. For the present study, to reduce the number of variables, and based upon our a priori hypotheses, only the Externalizing composite score, Internalizing composite score, and the Social Skills scale were used. The BASC was standardized using a sample of 2,231 children and 1,886 adolescents. The sample was nationally representative of gender, race/ethnicity, geographic location, and socioeconomic status. The child and adolescent versions of the PRS demonstrated good internal consistency, ranging from .90 to .95. The test-retest reliability ranged from .78 to .92 on the PRS child version and .83 to .90 on the PRS adolescent version. The BASC has satisfactory concurrent and discriminative validity as well (Doyle, Ostrander, Skare, Crosby, & August, 1997).

Exploratory Aim - Mediational Analyses Measures

Family Environment Scale-4th Edition (Moos & Moos, 1994).The Family Environment Scale (FES) is a 90-item true/false scale used to assess a parent's perception of the social environment of their family. There are 10 subscales on the FES measuring three dimensions: relationship, personal growth, and system maintenance. The relationship dimension assesses: 1) Family cohesion, the degree of support and commitment members of the family provide to each other; 2) Family expressiveness, the degree to which family members are encouraged to openly express themselves; and 3) Family conflict, the degree to which family

members openly express anger and aggression towards each other. The personal growth dimension assesses: 4) Independence, the degree to which family members are self-sufficient and make their own decisions; 5) Achievement orientation, the degree of activities family member are involved in that are motivated by achievement or competition; 6) Intellectual-cultural orientation, the degree of interest in political, intellectual, or cultural activities; 7) Active-recreational orientation, the degree to which family members are involved in social and recreational activities; and 8) Moral-religious emphasis, the degree of which the family puts emphasis on ethical or religious values. The system maintenance dimension assesses: 9) Family organization, the degree of planning put into family activities and responsibilities; and 10) Family control, the degree of rules and procedures instilled within the family. For the current study, only the FES relationship domain subscales (Cohesion, Expressiveness, Conflict) standard scores were used. Standard scores are produced for each of the three relationship subscales with higher scores indicating higher parent reported emphasis on that construct within the family. The FES is a well-validated instrument in adolescent populations and demonstrates adequate reliability, as measured by internal consistency (Boyd, Gullone, Needleman, & Burt, 1997; Robertson & Hyde, 1982).

Parenting Stress Index - 3rd Edition (Abidin, 1995). The Parenting Stress Index – 3rd edition (PSI-3) is a parent-report questionnaire designed to measure the amount of parental stress being experienced and to identify areas that are contributing to parental stress. The PSI-3 contains 101-items separated into two domains, parent characteristics and child characteristics. The Parent Domain has seven subscales, including Attachment, Competence, Depression, Parent Health, Relationship with Spouse, Restriction to Role, and Social Isolation. The Child Domain has six subscales, including Acceptability, Adaptability, Demandingness, Distractibility /

Hyperactivity, Mood, and Reinforces Parent. The items are rated on a five-point Likert scale from “strongly agree” to “strongly disagree,” with higher scores indicating higher parenting stress. Composite scores are provided for the Child Domain, Parent Domain, and Total Parent Stress. For the current study, we used all three domains as our parenting stress variables. The PSI-3 has good psychometric properties, including internal consistency of 0.90 and above for all three domains and good construct and discriminant validity (Abidin, 1995).

Procedures

Informed consent and assent was attained from parents and children. At all four time periods, a doctoral-level examiner administered all psychological tests to participants in a quiet room. Parents completed all parent-report rating scales in a separate room.

Planned Analyses

Analyses were conducted using SPSS-23.

Selection of outcome variables. The scores of the Time 4 SAS-SR Social and Leisure Activities Domain and the VABS-II Socialization scale were used separately as outcome variables. While this increases the likelihood of a Type I error rate, it is important that our outcome variables include both parent and self-report for several reasons. As described above, studies investigating social functioning in psychiatric and genetic disorders associated with 22q11.2DS have employed a wide and significantly diverse number of psychological scales used to measure social functioning. Since there is no gold-standard measure of social functioning outcomes, it is possible that the SAS-SR and the VABS-II may measure slightly different constructs in regards to social functioning outcomes. Likewise, given that these two scales are completed by two different raters, we were interested in examining if different variables would be predictive of social functioning outcomes relative to the perspective of the reporter. Including

both sources may provide useful information because it is possible that there may be differences in social functioning as a function of the reporter (self-report vs. parent-report). Lastly, investigating the predictors of the ability of individuals with 22q11.2DS to make and maintain friendships and relationships is a relatively new area of research with very few existing studies considering social functioning. Therefore, we sought to be as inclusive as possible.

Statistical power. Before conducting our analyses, we ran a power analysis to examine if our sample size was adequate. We conducted this testing using the statistical program, G power (Erdfelder, Faul, & Buchner, 1996). Using our cognitive regression model with the most variables (Specific Aim 3) to calculate the power analysis, and assuming a conservative effect size of 0.25 and alpha as 0.05, we entered 1 dependent variable (VABS-II Socialization) and 4 predictors (response inhibition, planning, working memory, cognitive flexibility) into G power. Results indicated that we needed 53 participants to achieve .80 statistical power. This means that our sample size is adequate to achieve good statistical power in 22q11.2DS, yet not in the other two groups. Having adequate power indicates that it is likely an effect will be detected when it is present, with a small probability of a Type II Error (failing to reject the null hypothesis when the effect is present.)

The significance or alpha level for all analyses was .05. We used an alpha level of .05 because correcting for multiple comparisons may have increased the type II error rate. Adjusting alpha weights may mask true statistical significance and increase the likelihood of null findings, which would not provide useful leads for future studies.

Data inspection. Before conducting analyses for each specific aim, outlier data points were truncated to 3 SDs above/below the group mean of each measure for each of the three groups (22q11.2DS, siblings, community controls). Truncating the distribution is a statistical

method commonly used to remove measurement error (Costa, 2014). This allowed for variables to be changed to less extreme but still high values as suggested by (Tabachnick & Fidell, 2007). This is an important step when conducting statistical analyses, as an outlier can influence the mean of the distribution and lead to false conclusions (e.g., Type I Error/Type II Error). In our sample, a total of 10 scores were truncated: 4 participants with 22q11.2DS, 3 siblings, and 3 controls. In addition, our data were examined for missing values and all analyses were treated using list-wise deletion, a decision that has precedent in the literature and is recommended by experts (Peugh & Enders, 2004). Finally, considering our small group sample sizes and the likelihood that missing data would reduce statistical power, when conducting regression analyses, mean substitutions were used. This decision also has precedent in the literature and is recommended by experts (Raaijmakers, 1999).

Specific aim 1. A one-way analysis of variance (ANOVA) will be used to assess if mean differences existed in social functioning for individuals with 22q11.2DS, siblings and controls at Time 4 (young adulthood). A one-way ANOVA will also be conducted using weighted means due to the uneven sample sizes between groups. Lastly, given the prevalence of cognitive delays among individuals with 22q11.2DS, an analysis of covariance (ANCOVA) will be used to examine the mean differences in social functioning between groups while controlling for full-scale IQ. Tukey post-hoc tests will be conducted to identify the groups that have a significant mean difference. Homogeneity of variance was tested using Levene's Test for Equality of Variances for between subject's comparisons. Mauchly's Test of Sphericity was used to test for equal variances of the differences between all the groups, known as sphericity, for within subjects comparisons of social functioning across time.

Multicollinearity and Normal Distributions. Before conducting any regression analyses for specific aims 2, 3 and 4, multicollinearity was assessed by examining the correlation matrix between variables. Multicollinearity is important to test because it suggests that the high correlation between individual variables can increase the variance of the model and result in a lack of statistical significance when the individual predictor should be significant (Type II Error), thus leading to inaccurate conclusions. A correlation coefficient of *.80* was used as a cutoff, as suggested by (Tabachnick & Fidell, 2007) because a strong correlation suggests that the variables are measuring the same/very similar constructs. In addition, multicollinearity diagnostics were also conducted for every regression analysis using variance inflation factor (VIF). The VIF is an index of how much variance of a regression coefficient is increased due to multicollinearity and is a widely used method of detecting multicollinearity (Montgomery, 2001). As suggested by (Montgomery, 2001) a predictor that has a VIF greater than 5 should be further investigated. Based on the correlation matrix and VIF (included in all regression tables), none of our models demonstrated multicollinearity.

In addition, the skewness of Time 4 social functioning was evaluated. For the 22q11.2DS group, the parent-reported social functioning outcome variable had skewness of .018 (*SE* = .327) and kurtosis of .182 (*SE* = .644) and self-reported social functioning had skewness of .514 (*SE* = .330) and kurtosis of .178 (*SE* = .650). In the sibling group, the parent-reported social functioning outcome variable had skewness of .290 (*SE* = .536) and kurtosis of -1.190 (*SE* = 1.038) and self-reported social functioning had skewness of 1.352 (*SE* = .550) and kurtosis of 2.688 (*SE* = 1.063). The community control group parent-report of social functioning had skewness of -.302 (*SE* = .564) and kurtosis of -1.288 (*SE* = 1.091) and self-reported social

functioning had skewness of .794 (*SE* = .580) and kurtosis of -.742 (*SE* = 1.121). As indicated by West, Finch, and Curran (1995) these variables appear to be normally distributed.

Specific aim 2. Specific aim 2 will only be considered in the 22q11.2DS group. Zero-Inflated Poisson (ZIP) regression analyses (Lambert, 1992) will be conducted in the 22q11.2DS group using the SIPS Positive Symptoms Score to assess the relationship between Time 4 positive symptoms of psychosis and our outcome measures of Time 4 social functioning, the VABS-II Socialization and SAS-SR. A ZIP regression was used due to the non-normal distribution of our SIPS Positive Symptoms scores, many of which were, "0" indicating no positive psychotic symptoms present. The proportion of zeros in the SIPS Positive Symptom variable was greater than the proportion of non-zeros, thus necessitating the use of ZIP regression analyses to account for excess zeros. A Vuong test, conducted to determine if the proportion of scores equaling zero warranted using a Zero-Inflated Poisson (ZIP) regression model, was significant for both the VABS-II Socialization ($z = 2.58$, $p = .005$) and SAS-SR Social and Leisure Activities ($z = 2.93$, $p = .002$), indicating that the ZIP regression model was appropriate.

Specific aim 3. Three separate multiple linear regression model analyses will be used to determine if social functioning could be predicted from general intelligence assessed by the WISC-III FSIQ from Time 1 (Specific Aim 3a) or Time 1 executive functioning abilities (Specific Aim 3b) for individuals with 22q11.2DS, CC or siblings. Multiple linear regression was used to assess how much variance in social functioning could be explained by predictor variables. The regression will produce F-statistics which will be used to calculate *p*-values. Beta weights will be also provided for each predictor to indicate the direction of change in the outcome variable for one unit difference in the predictor. Significant *p*-values will be used to

determine which values are significant predictors and beta weights were used to examine the strength of the relationship.

Executive functioning composite scores. Since more than one psychological test score was used in our study to assess response inhibition, cognitive flexibility, and working memory, average z-scores were created for each of these executive functioning domains. More specifically, the mean of z-scores for the Gordon Diagnostic System and the Stroop Color-Word Test were used to create an average z-score for response inhibition. Cognitive flexibility was assessed using the average z-score of the Stroop Color-Word Test and the Wisconsin Card Sorting Test. A mean working memory z-score was created using the California Verbal Learning Test, Visual Span Test, and the WISC-III Freedom from Distractibility Composite. Since we only used the Tower of London scores to assess planning, an average z-score was not created for this domain of executive functioning (Figure 3).

The rationale for creating z-scores for each domain of executive functioning was to decrease the Type I error rate caused by conducting multiple analyses. Also, creating z-scores made our analyses consistent by allowing us to enter all of the same variables into the cognitive regression models for each of the three groups: 22q11.2DS, siblings, and community controls. Like any statistical method, there are limitations to conducting analyses using composite scores. For instance, for efficiency reasons, each subcomponent of executive functioning is commonly assessed in clinical settings using only one instrument; therefore, creating total scores may hinder the ability for our results to generalize in clinical settings when examining cognitive abilities for treatment purposes. However, being that research examining the relationship between executive functions and social functioning in 22q11.2DS is a relatively limited research area, and there are methodological issues with only using one instrument for each subcomponent of executive

functioning (Snyder et al., 2015), we elected to create composite scores based upon multiple tests of the same construct. According to Snyder et al. (2015) there is a task-impurity problem when measuring executive functioning, such that all tasks include variance caused by non-executive functioning cognitive processes associated with the content of the task (e.g., reading decoding in the Stroop task). However, by combining data from multiple measures of executive functions into a z-mean score instead of only using one instrument, the variance of non-executive functioning processes is reduced (Snyder et al., 2015).

Covariates. Within our multiple linear regression models, we added several covariates to control for the effects of these constructs on our model. Social functioning at time 1 was entered as a covariate to account for the variance that reported levels of social functioning in childhood may have on social functioning outcomes in adulthood. Due to social deficits reported in previous research within 22q11.2DS, it is possible that poor social functioning scores at time 1 (childhood) will drive poor social functioning outcomes at time 4 (young adulthood). By entering parent reported social functioning at time 1 as a covariate, however, we aim to identify what other cognitive constructs may be contributing to parent reported social functioning. We did not covary for time 1 social functioning in models with time 4 self-reported social functioning (SAS-SR Social and Leisure Activities) as the outcome measure because we did not collect a self-reported measure of social functioning at time 1. This decision is supported by the low to moderate associations noted between parent- and self-report of social functioning (22q11.2DS r = -.44, siblings r = -.06, and community controls r = -.42) indicating that they may be measuring slightly different constructs. (The directions are negative due to high scores on the SAS-SR indicating social functioning impairments while low scores on the VABS-II indicate low social functioning.)

Also, due to the inherent cognitive deficits associated with 22q11.2DS, Verbal IQ was also entered into the model. Adding Verbal IQ as a covariate allows us to account for the variance verbal abilities may have on an individual's ability to make or maintain relationships with others. Verbal IQ was chosen as a covariate instead of FSIQ or nonverbal IQ because language skills are a construct more closely related to social functioning (Liss et al., 2001). Some researchers argue against using IQ as a covariate in studies of individuals with neurodevelopmental disorders because IQ scores in neurodevelopmental disorders postdate the condition, meaning that these individuals have experienced atypical development since birth and therefore diminished cognitive abilities can not be separated from the disorder (Dennis et al., 2009). For the purposes of this study, however, we sought to identify the constructs most contributing to social functioning difficulties to provide useful information for intervention within 22q11.2DS and covaried for Verbal IQ at Time 1 in our models. In this way, we can consider both the contribution of Verbal IQ and which components of executive functioning measured in childhood may best predict social functioning later in life.

Specific aim 4. Next, 3 separate multiple linear regression analyses will be conducted to determine if young adult social functioning could be predicted from childhood behavioral and emotional functioning as well as emotion recognition constructs in 22q11.2DS, CC and siblings. Behavioral predictors were assessed using the BASC - Parent Rating Scale, and emotion recognition was assessed using the Penn Emotion Recognition Test.

Covariates. We again added several covariates within our multiple linear regression models for specific aim 4 to control for the effects of these constructs on our model. Due to the findings of poor childhood social functioning in previous 22q11.2DS studies, we entered social functioning at time 1 as a covariate to account for the variance that childhood social functioning

may have on social functioning outcomes in young adulthood, in order to identify what other behavioral/emotional constructs may be contributing to parent reported social functioning. We did not covary for time 1 social functioning in models with time 4 self-reported social functioning (SAS-SR Social and Leisure Activities) for the reasons identified above. Verbal IQ was again entered into the regression models for specific aim 4 to account for the variance verbal abilities may have on social functioning outcomes.

Exploratory aim 1. If significant childhood cognitive and behavioral / emotional predictors of young adult social functioning emerged in Specific Aims 3 and 4, mediation analyses will be conducted to examine if adolescent (Time 2) family environment or factors contributing to parental stress mediated the relationship (Exploratory Aim 1). These analyses aim to provide more information about the potential causal relationship between the predictor and social functioning. It is possible that family environment in adolescence is influenced by cognitive, behavioral, or emotional challenges presented by children and may be a mechanism affecting poor social outcomes in adulthood. Likewise, parents play a large role in their children's social experiences and it is possible that factors contributing to higher parental stress in adolescence are a mechanism influencing social functioning outcomes later in life. To test the proposed indirect effects model suggesting that the association between the identified cognitive, behavioral, or emotional predictors and social functioning may be due, at least in part, to family environment or parenting stress, a mediation approach of bootstrapping the indirect effect was used (Preacher & Hayes, 2004, 2008). Bootstrapping is a resampling procedure in which a repeated series of representations are created from the current sample in an attempt to recreate the original sampling procedure. For every resample, the a and b path and indirect effect are estimated and the distribution of these estimated indirect effects functions as an approximation of

the sampling distribution of the indirect effect. For the current study, the number of bootstrapping samples was set to 1,000 and these samples were used to generate a 95% confidence interval for the indirect effect. A confidence interval that does not include zero is considered statistically significant. Bootstrapping widely considered one of the more powerful and valid methods of testing mediation (Williams & MacKinnon, 2008).

For these analyses, the SPSS-23 mediation PROCESS macro described in (Hayes, 2013) was used. PROCESS is a widely used statistical tool for mediation analysis freely available at *www.processmacro.org.* This approach differs from the commonly used causal steps approach proposed by Baron and Kenny (1986), which requires that each of the paths of the model meet statistical criteria. For example, in a simple mediation model, a path and b path need to be statistically significant, and c' path should be closer to zero than c path to consider a variable as a mediator between the predictor and outcome variables. Fritz and MacKinnon (2007) suggest that this causal steps approach is arguably low in power and has been criticized for being the least likely to detect mediation effects. Hayes (2009) argues that the causal steps approach has too many null hypotheses to reject and by minimizing the number of tests, the indirect effect is more likely to be found. Based upon these factors, we elected to use the Preacher and Hayes (2004, 2008) method for assessing mediation.

Results

Variable Relationships

Pearson correlation coefficients for all variables used in each specific aim are presented in Tables 5 (22q11.2DS group), 6 (Siblings) and 7 (Community Controls). As noted in these three tables, other than WISC-III composites correlating strongly with each other, all other relationships were small to moderate in size.

Young adult social functioning associations. There was a moderate negative relationship between the parent-reported VABS-II socialization scale and the self-reported SAS social and leisure activities domain, $r(83) = -.356$, $p = .01$, with all participants included. (This relationship is negative because lower scores on the VABS-II and higher scores on the SAS-SR are both indicative of more impairment.) When examining the correlations separately for each group, the VABS-II socialization scale and SAS-SR social and leisure activities domain were moderately correlated for the 22q11.2DS group ($r(51) = -.442$, $p = .001$) and for the community control group ($r(15) = -.417$, $p = .122$), and there was a weak relationship between these variables for the sibling group ($r(17) = -.062$, $p = .812$). A moderate relationship indicates that the scales are associated but that they are measuring different constructs. Therefore, both the socialization scale of the VABS-II and the social and leisure activities domain of the SAS-SR were used separately as outcome measures for the analyses.

Specific Aim 1

Young adult social functioning group differences. A one-way ANOVA was conducted to examine differences in parent-reported social functioning at Time 4 between the 22q11.2DS, sibling, and CC groups. There was homogeneity of variance between the three groups as assessed by Levene's Test for Equality of Variances for both Time 4 parent-reported VABS-II Socialization scale ($F = 1.13$, $p = .327$) and Time 4 SAS-SR social and leisure activities ($F = 0.23$, $p = .795$).

There was a statistically significant difference in the parent-reported VABS-II Socialization scale at Time 4 among the three groups, $F(2,84) = 38.2$, $p < 0.001$. As seen in Table 8, Tukey post-hoc tests suggest that parents of participants with 22q11.2DS reported significantly lower social functioning (M = 68.9, SD = 13.4) than both the sibling (M = 95.8, SD

= 12.8) and CC groups (M = 94.9, SD = 15.9) (Figure 1). The siblings and CC groups did not differ from each other.

When a one-way ANOVA was conducted using weighted means to control for unequal sample sizes, there was still a statistically significant difference in the parent-reported VABS-II Socialization scale at Time 4 among the three groups, F (2,134) = 57.6, $p < 0.001$, with parents rating individuals with 22q11.2DS lower (M = 68.9, SD = 13.4) than both siblings (M = 95.8, SD = 12.6) and community controls (M = 94.9, SD = 15.5). Likewise, when an analysis of covariance was conducted, there was still a group effect (22q11.2DS, siblings, CC) on parent reported social functioning after controlling for FSIQ, F (2,83) = 8.47, $p < 0.001$, suggesting that general cognitive abilities do not explain the differences in social functioning as reported by parents.

Conversely, a one-way ANOVA comparing all domains of the self-report SAS-SR social and leisure activities across the 22q11.2DS, sibling, and CC groups revealed that there were no significant differences between the three groups ($p > .05$). In addition, SAS-SR work, relationships with extended family, role as a spouse or partner, parental role, and role within the family unit domains all failed to reach statistical significance (p's > .05) (Table 8).

When a one-way ANOVA was conducted using weighted means to control for unequal sample sizes, there was a statistically significant difference in the SAS-SR social and leisure activities at Time 4 among the three groups, F (2,128) = 4.11, $p < 0.05$, with individuals with 22q11.2DS self-reporting poorer social functioning (M = 58.2, SD = 10.5) than siblings (M = 52.1, SD = 10.9), but not community controls (M = 56.8, SD = 7.9). However, when an analysis of covariance was conducted, there was not a significant group effect (22q11.2DS, siblings, CC) on parent reported social functioning after controlling for FSIQ ($p > .05$), which suggests that

general cognitive abilities impacted how individuals rated their social functioning.

Paired samples t-tests were conducted to examine if significant differences existed between parent-report and self-report measures within each group. There was a significant difference between the VABS-II Socialization scale and the SAS-SR social and leisure activities domain within the 22q11.2DS group t (50) = -14.623, p = .0001 and sibling group t (16) = -2.442, p = .027, but not the community control group (p > .05) (Figure 1).

A repeated measures ANOVA was conducted to examine the effect of time on the VABS-II Socialization scale, measured at all four time points. Mauchly's Test of Sphericity indicated that the assumption of sphericity was violated, X^2 (5) = 14.981, p = .01, and therefore, a Greenhouse-Geisser correction was used. The interaction between time and group (22q11.2DS, sibling, CC) failed to reach statistical significance, F (6, 204) = .339, p = .898 (Figure 2). There was also no significant effect of time on the VABS-II Socialization scale, F (3, 204) = .671, p = .553. Thus, VABS-II socialization ratings were relatively constant across time in all three groups indicating that parent rated 22q11.2DS social functioning impairments are consistent across time. SAS-SR social and leisure activities data was not collected at Time 1. Thus, this analysis could not be performed for self-report data.

Specific Aim 2

Psychosis and social functioning. The mean SIPS Positive Symptoms Score for the 22q11.2DS group was 3.3 (SD = 5.39), with 48% of individuals reporting at least one positive symptom of psychosis, leaving 52% of scores as zero (indicating no positive symptoms of psychosis). A Vuong test, conducted to determine if the proportion of scores equaling zero warranted using a Zero-Inflated Poisson (ZIP) regression model, was significant for both the VABS-II Socialization (z = 2.58, p = .005) and SAS-SR (z = 2.93, p = .002), indicating that the

ZIP regression model was appropriate. The ZIP regression conducted for the 22q11.2DS group that examined if Time 4 VABS Socialization scores predicted Time 4 SIPS Positive Symptoms Score was significant (z = -4.49, p = .0001). In 22q11.2DS, the model examining if SAS-SR social and leisure activities predicted SIPS Positive Symptoms Score was also significant (z = 4.27, p = .0001). Thus, from both parent and self-report, higher levels of Time 4 positive psychotic symptoms were associated with lower Time 4 social functioning. Given these relationships, if any significant findings emerge in Specific Aims 3 and 4 in the 22q11.2DS group, the possible role of positive symptoms of psychosis will be considered as a possible explanatory variable for the significant findings.

Specific Aim 3

Childhood cognitive variable group differences. A multivariate analysis of variance (MANOVA) was conducted using childhood cognitive variables. There was a significant multivariate effect, $F(26,84) = 4.145$, $p < .001$; Wilk's $\lambda = 0.192$, partial $\eta^2 = 0.56$. As shown in Table 9, univariate results showed significantly lower performance for the 22q11.2DS group than both the sibling group and CC group for most cognitive variables including the WISC-III FSIQ ($F(2,54) = 35.95$, $p < .001$, partial $\eta^2 = .57$), WISC-III Freedom from Distractibility ($F(2,52) = 12.01$, $p < .001$, partial $\eta^2 = .31$), WISC-III Verbal IQ ($F(2,54) = 21.42$, $p < .001$, partial $\eta^2 = .44$), WCST perseverative errors ($F(2,54) = 19.95$, $p < .001$, partial $\eta^2 = .43$), CVLT List A Trial 1 ($F(2,54) = 5.13$, $p = .009$, partial $\eta^2 = .16$), CVLT List A Trial 5 ($F(2,54) = 5.83$, $p = .005$, partial $\eta^2 = .18$), Visual Span Test Forward Span ($F(2,54) = 18.28$, $p < .001$, partial $\eta^2 = .40$), and Visual Span Test Backward Span ($F(2,54) = 8.33$, $p = .001$, partial $\eta^2 = .24$).

The 22q11.2DS group had significantly lower scores than siblings but not CCs on the GDS commission errors ($F(2,54) = 3.27$, $p = .046$, partial $\eta^2 = .11$). Likewise, the 22q11.2DS

group demonstrated significantly worse performance on the Tower of London ($F(2,54) = 4.94$, $p = .011$, partial $\eta^2 = .16$) than siblings but not CCs. There were no significant childhood differences between groups for Time 1 WCST non-perseverative errors, Stroop interference scores, and CVLT List B scores.

Specific Aim 3a - Regression analyses of childhood general intelligence. Linear regression analyses examining the relationships between IQ and social functioning were conducted for each group separately controlling for Time 1 social functioning in step one. In the 22q11.2DS group, the majority of the variance explained in the model was accounted for in step 1 (Time 1 Vineland Socialization; $r^2 = .307$, $F(1,51) = 22.61$, $p < .0001$). Step 2 (Time 1 FSIQ) was not significant after controlling for the effects of Time 1 Vineland Socialization. See Table 10 for 22q11.2DS results.

In the sibling group, step 1 (Time 1 Vineland Socialization) was non-significant and the model remained non-significant in Step 2 (FSIQ) $p > .05$ (Table 11). Lastly, in the CC group, the majority of the variance explained was accounted for in step 1 (Time 1 Vineland Socialization; $r^2 = .366$, $F(1,14) = 8.10$, $p = .013$). Step 2 (FSIQ) was not significant after controlling for the effects of Time 1 Vineland Socialization (Table 12). Thus, in all 3 groups, childhood FSIQ did not predict young adult social functioning after controlling for Time 1 social functioning. In the 22q11.2DS and CC groups (yet not the siblings), parent reported Time 1 social functioning was a significant predictor of parent reported Time 4 social functioning.

When Time 4 Vineland was used as the outcome variable, but Time 1 social functioning was not included as a covariate, the models for the 22q11.2DS group, sibling group, and CC groups were non-significant ($p > .05$). This suggests that childhood FSIQ does not independently predict social functioning outcomes in young adulthood. Time 1 FSIQ was not significantly

correlated with the Time 4 socialization scale of the VABS-II for the 22q11.2DS (r = .20), sibling (r = .27) or community control (r = .38) groups. Thus, childhood FSIQ was not a predictor of parent-reported young adult social functioning, nor significantly associated with young adult social functioning in any group.

Similarly, when the SAS-SR social and leisure activities was used as the outcome variable, the models were non-significant for all three groups (p > .05). Time 1 Vineland Socialization (parent-report) was not included as a covariate in these models because the SAS-SR is completed by a different rater (self-report) and these measures are only moderately correlated. Overall, Time 1 FSIQ was not a significant predictor of Time 4 social functioning self-reports in all three groups.

Specific Aim 3b - Executive functioning composite variables. In our study, multiple measures were used to assess the same constructs within executive functioning (response inhibition, working memory, and cognitive flexibility). Our analyses included 6 possible measures of working memory (Freedom from Distractibility Composite, CVLT List A trial 1, List A trial 5, List B, and Visual Span Test Forward and Backward Span scores), 2 possible measures of response inhibition (GDS Commission Errors and Stroop Color-Word Test Interference score), and 3 possible measures of cognitive flexibility (WCST Perseverative Errors, WCST Non-perseverative Errors, and Stroop Color-Word Test Interference Score). As seen in Figure 3, composite z-mean scores were created for each domain of executive functioning. First, the Freedom from Distractibility Composite, the Stroop Color-Word Test Interference score, and the WCST Perseverative Errors and Non-perseverative Errors were transformed into z scores using the population mean. Only the scores from these measures were transformed because z-scores were already being used for all other cognitive measures. Composite scores were created

using a mean of all z-scores for each domain of executive functioning. Hence, all regression analyses for each group, 22q11.2DS, siblings, and CC, included a working memory, response inhibition, and cognitive flexibility composite variable. Our study included only one measure of planning (Tower of London Total moves). Therefore, there was no composite score created for the planning.

22q11.2DS group executive functioning. In the 22q11.2DS group, when using Time 4 Vineland Socialization Scale as the outcome variable, the majority of the variance explained was accounted for in step 1 (Time 1 Vineland Socialization; $r^2 = .307$, $F(1,51) = 22.61$, $p < .0001$). Step 2 (Verbal IQ) and step 3 (Executive Function mean z-score scores) were not significant after controlling for the effects of Time 1 Vineland Socialization ($p > .05$). Time 1 VABS-II Socialization made a significant contribution to predicting time 4 VABS-II socialization ($\beta = .54$, $p < .001$), but after controlling for this variable, no other variable made a significant contribution. (Table 13).

In the 22q11.2DS group, using the self-reported social functioning measure (SAS-SR social and leisure activities domain) as the outcome variable, neither Step 1 (Verbal IQ) nor Step 2 (Executive Function mean z-score scores) were significant predictors of Time 4 self-ratings ($p > .05$) (Table 14).

Sibling group executive functioning. In the sibling group, when using Time 4 Vineland Socialization Scale as the outcome variable, step 1 (Time 1 Vineland Socialization), step 2 (Verbal IQ) and step 3 (Executive Function mean z-score scores) were each not significant ($p > .05$) (Table 15).

The regression analysis for siblings including the SAS-SR social and leisure activities domain as the outcome variable indicated that step one (Verbal IQ) was not significant ($p > .05$).

Step 2 (Executive Function mean z-score scores; r^2 = .533, F(4,12) = 3.43, p = .043) was significant. Of the executive functioning variables examined in step 2, only Time 1 planning made a unique contribution to predicting time 4 SAS-SR social and leisure activities (β = .88, p = .009). (Table 16).

Community control group executive functioning. In the CC group, when using Time 4 Vineland Socialization Scale as the outcome variable, the majority of the variance explained was accounted for in step 1 (Time 1 Vineland Socialization; r^2 = .366, F(1,14) = 8.10, p = .013). Step 2 (Verbal IQ) and step 3 (Executive Function mean z-score scores) were not significant after controlling for the effects of Time 1 Vineland Socialization (p > .05) (Table 17).

Using the self-reported social functioning measure (SAS-SR social and leisure activities domain) as the outcome variable, neither step 1 (Verbal IQ) nor step 2 (Executive Function mean z-score scores) were significant predictors of Time 4 self-ratings (p > .05) (Table 18).

Specific Aim 4

Childhood behavioral / emotional variable group differences. A MANOVA was conducted using childhood behavioral and emotional predictors. As shown in Table 19, there was a significant multivariate effect (F(8,150) = 5.07, p < .001; Wilk's λ = 0.590, partial η^2 = .23). Univariate results showed significantly lower scores for the 22q11.2DS group than both the sibling group and CC group on the Penn Emotion Recognition Test (F(2,78) = 9.43, p < .001 partial η^2 = .20), indicating poorer abilities to accurately recognize emotions in others. Significantly lower scores for the 22q11.2DS group than both the sibling group and CC group was also found on the BASC social skills composite (F(2,78) = 13.13, p < .001, partial η^2 = .25), which indicates a lower parent reported frequency of socially skilled behaviors in childhood. On the BASC-PRS Internalizing composite, the 22q11.2DS group had significantly higher scores

than both the sibling group and CC group ($F(2,78) = 11.25$, $p < .001$, partial $\eta^2 = .22$), which indicates more parent reported internalizing symptoms in childhood. Lastly, the 22q11.2DS group had significantly higher scores when compared to the CC group, but not the sibling group on the BASC Externalizing composite ($F(2,78) = 4.46$, $p = .015$, partial $\eta^2 = .10$).

Regression analyses of childhood behavioral / emotional variables.

***22q11.2DS group behavioral/emotional models*.** In the 22q11.2DS group, when using Time 4 Vineland Socialization Scale as the outcome variable, the majority of the variance explained was accounted for in step 1 (Time 1 Vineland Socialization; $r^2 = .307$, $F(1,51) = 22.61$, $p < .0001$). Step 2 (Verbal IQ) was not significant. Step 3 (Time 1 Behavioral and Emotional scores; $r^2 = .153$, $F(4,46) = 3.26$, $p = .019$) made a significant contribution to predicting Time 4 Vineland socialization. The overall model accounted for 46.1% of the variance in Time 4 Vineland socialization. Of the behavioral/ emotional variables included, only BASC internalizing behaviors ($\beta = -.38$, $p = .005$) significantly predicted young adult social functioning in 22q11.2DS (Table 20).

In the 22q11.2DS group, using the self-reported social functioning measure (SAS-SR social and leisure activities domain) as the outcome variable, neither Step 1 (Verbal IQ) nor Step 2 (Behavioral and Emotional scores) were significant predictors of Time 4 self-ratings ($p > .05$) (Table 21).

Follow up analyses. Since a significant relationship was previously demonstrated between Time 4 SIPS Positive symptoms and Time 4 Vineland Socialization (Specific Aim 2), and Time 1 BASC internalizing symptoms seem to be making a significant contribution to Time 4 Vineland Socialization in the 22q11.2DS group, we sought to further examine the relationship between Time 1 BASC internalizing symptoms and Time 4 SIPS Positive Symptoms. The ZIP

regression conducted within the 22q11.2DS group that examined if Time 1 BASC internalizing symptoms predicted Time 4 SIPS Positive Symptoms Score was not significant (z = -1.46, p = 144). Thus, childhood parent reported internalizing symptoms are not a significant predictor of positive symptoms of psychosis in adulthood.

To further understand any contributions of concurrent positive symptoms of psychosis to our longitudinal findings, a second regression analysis was then used to examine the extent to which childhood internalizing symptoms predict young adult social functioning, after controlling for young adult positive symptoms of psychosis. In this stepwise regression, when using Time 4 Vineland Socialization Scale as the outcome variable, step 1 was significant (Time 1 Vineland Socialization; r^2 = .339, F(1,45) = 23.13, p < .0001). Step 2 (Verbal IQ) was not significant. Step 3 (Time 4 SIPS Positive Symptoms; r^2 = .108, F(1,43) = 8.52, p = .006) was significant and step 4 was also significant (Time 1 BASC internalizing symptoms; r^2 = .071, F(1,42) = 6.28, p = .016. The overall model accounted for 47.9% of the variance in Time 4 Vineland socialization. Therefore, even after controlling for positive symptoms of psychosis at time 4, parent reported childhood internalizing symptoms continue to make a significant contribution to explaining the variance in young adult social functioning in the 22q11.2DS group.

Sibling group behavioral/emotional models. In the sibling group, when using Time 4 Vineland Socialization Scale as the outcome variable, neither step 1 (Time 1 Vineland Socialization), step 2 (Verbal IQ) nor step 3 (Time 1 Behavioral and Emotional scores) predicted Time 4 parent-ratings (p > .05) (Table 22). When the SAS-SR was used as the outcome measure, step 1 (Verbal IQ) was not significant (p > .05). Step 2 (Time 1 Behavioral and Emotional scores; r^2 = .153, F(4,46) = 3.26, p = .021) made a significant contribution to predicting the Time 4 SAS-SR social and leisure activities domain. Of the behavioral and emotional variables

examined, only parent reported BASC social skills in childhood were a significant predictor of Time 4 self-reported social functioning (β = .83, p = .015) (Table 23).

Community control group behavioral/emotional models. In the CC group, when using Time 4 Vineland Socialization Scale as the outcome variable, the majority of the variance explained was accounted for in step 1 (Time 1 Vineland Socialization; r^2 = .366, F(1,14) = 8.10, p = .013). Neither Step 2 (Verbal IQ) nor step 3 (Time 1 Behavioral and Emotional scores) was significant after controlling for the effects of Time 1 Vineland Socialization (p > .05). (Table 24) When the SAS-SR social and leisure activities was used as the outcome measure, neither step 1 (Verbal IQ) nor step 2 (Time 1 Behavioral and Emotional scores) was significant (p > .05) (Table 25).

Exploratory Aim 1 - Mediation Analyses

Given our significant findings in Specific Aim 4 for the 22q11.2DS group for Time 1 BASC internalizing behaviors, our exploratory aim was investigated. Prior to analyzing the mediation analyses, group differences were examined for our two proposed mediators, adolescent family environment and parenting stress.

Family environment and parent stress group differences. A MANOVA was conducted comparing Time 2 (adolescence) family environment and parenting stress between the three groups. There was a significant multivariate effect (F(12,116) = 3.646, p < .001; Wilk's λ = 0.527, partial η^2 = .25). As shown in Table 26, univariate results showed significantly higher scores for the 22q11.2DS group than the CC group, but not the sibling group on the PSI total parent stress domain (F(2,59) = 6.60, p = .002, partial η^2 = .18) and higher scores for the 22q11.2DS group than both the sibling and CC group on the PSI child stress domain (F(2,59) = 15.81, p < .001, partial η^2 = .36). These results indicate that the parents of youth with 22q11.2DS

report that their children have problematic behaviors that make parenting stressful. There were no significant differences between groups for the PSI parent domain and all domains of the Family Environment Scale – 4th Edition (cohesion, conflict, and expressiveness).

Mediational analyses. In the 22q11.2DS group, mediation analyses were performed to investigate the hypotheses that various domains of family environment (Time 2 cohesion, expressiveness, conflict) and parenting stressors in adolescence (Time 2 total parent stress, child domain, parent domain) mediate the relationship between Time 1 BASC internalizing behaviors and young adult parent-reported social functioning (Time 4 VABS-II Socialization scale). The indirect effect was tested using a bootstrap estimation approach with 1000 samples.

Specifically, as seen in Table 27, results showed that parent reported BASC internalizing behaviors were a significant predictor of the PSI child domain (β = .63, SE = .23, p = .008) and that the PSI child domain approached significance as a predictor of VABS-II Socialization (β = -.17, SE = .09, p = .053). BASC internalizing behaviors were a significant predictor of VABS-II Socialization (β = -.41, SE = .13, p = .004). The indirect coefficient was significant (β = -.11, SE = .09, 95% CI = -.3705, -.0048) (Figure 4); these results support a partial mediational hypothesis. Therefore, parents of youth with 22q11.2DS report increases in internalizing behaviors in childhood (T1) and increased problematic behaviors that cause parenting stress in adolescence (T2), which in turn lower parent-report social functioning scores in young adulthood (T4).

Using the VABS-II Socialization scale as the outcome variable, FES cohesion, FES expressiveness, FES conflict, PSI parent stress, and PSI total stress were not significant mediators. Likewise, there were also no significant mediators in analyses conducted with SAS-SR social and leisure activities domain as the outcome variable.

Discussion

The present study highlights social functioning impairment etiologies that may be specific to 22q11.2DS and, to our knowledge, is the first longitudinal study to identify childhood factors that may contribute to poor social functioning outcomes in young adulthood for individuals with 22q11.2DS. In summary, childhood internalizing symptoms prospectively predicted social functioning outcomes in young adulthood in 22q11.2DS, even after controlling for the influences of poor social functioning in childhood, verbal abilities in childhood, and positive symptoms of psychosis in young adulthood. Interestingly, general intelligence and executive functioning in childhood did not significantly predict social functioning outcomes indicating that symptoms of anxiety, depression and somatization in childhood better predict the social difficulties common in 22q11.2DS in young adulthood. High parenting stress from problematic behaviors displayed by individuals with 22q11.2DS in adolescence mediated the relationship between elevated internalizing symptoms in childhood and low social functioning in young adulthood.

Specific Aim 1: Parent and Child Perceptions of Social Functioning

Overall, parents rated individuals with 22q11.2DS as having more social difficulties than siblings and community controls across all four time points from childhood to young adulthood. This is consistent with previous 22q11.2DS research suggesting that children with 22q11.2DS exhibit poor social functioning when compared to same-age peers (Shashi et al., 2012; Swillen et al., 1997). Parents of participants with 22q11.2DS described their children having more difficulty with interpersonal relationships, seeking out social activities, and demonstrating proper coping skills in social settings during all developmental periods (T1 to T4). Our results are remarkably similar to those reported by Butcher et al. (2012), with both groups reporting that parent reported

social functioning in adults with 22q11.2DS is greater than 2 standard deviations below the mean.

Within groups, parent and child report of child social functioning were moderately associated with each other in the 22q11.2DS and community control groups (*r*'s = -.4 range) yet not related with each other in the sibling group. Despite these moderate relationships in the 22q11.2DS group, individuals with 22q11.2DS reported having statistically comparable social functioning levels with the other two groups. While parent and child reports of child functioning are not collinear (Kolko & Kazdin, 1993), the lack of a self-report group difference (despite significant group differences in parent report) is interesting. Our data suggest that unlike their parents, individuals with 22q11.2DS do not perceive themselves as experiencing social difficulties when compared to their same aged peers.

One possible explanation for the lack of self-report differences between the three groups may be related to cognitive immaturity (Milich, 1994). Cognitive immaturity has been forwarded as a hypothesis to explain the commonly noted positive self-perceptions that exist in ADHD (Owens, Goldfine, Evangelista, Hoza, & Kaiser, 2007). Given the cognitive abilities of individuals with 22q11.2DS in our sample (mean FSIQ = 70), and the lack of a significant difference in self-reported social functioning among groups when controlling for FSIQ, the cognitive immaturity hypothesis suggests that developmental delays may explain these findings. Without a developmentally-matched control group, it is not possible to ascertain to what extent this finding (no self-reported differences) is specific to 22q11.2DS. The differences in social functioning scores between reporters in our sample may also be due to parents comparing their children to typically developing individuals of the same chronological age (e.g., siblings) when completing the VABS-II, which would cause parents to report lower perceptions of social

functioning. Just as others in the ADHD literature (Swanson, Owens, & Hinshaw, 2012) have encouraged researchers not to consider that parents are correct (and children are incorrect), future research should continue to investigate how parent- and self-report of social functioning in 22q11.2DS are related and how best to understand any differences that may exist between reporters.

Specific Aim 2: Psychosis and Social Functioning in Young Adulthood

Given that approximately one third of individuals with 22q11.2DS develop schizophrenia (Drew et al., 2011) and a prodromal period of social withdrawal and isolation typically precedes the onset of psychotic symptoms in schizophrenia, we examined how symptoms of psychosis were related to the social impairments exhibited in young adults with 22q11.2DS. Within our sample, approximately 48% of individuals with 22q11.2DS endorsed positive symptoms of psychosis and elevated positive symptoms of psychosis in young adulthood (Time 4) were related to lower parent-report and self-report of social functioning (Time 4). These results supported our hypothesis and are a finding consistent with previous research in 22q11.2DS (Butcher et al., 2012) and schizophrenia literature (Burns & Partick, 2007).The relationship between poor social premorbid adjustment and psychosis has also been identified cross-sectionally in 22q11.2DS (Yuen et al., 2013).

However, Radoeva et al. (2016) did not find a significant longitudinal relationship between poor social premorbid adjustment in childhood, early adolescence, or late adolescence with symptoms of psychosis in adulthood. Therefore, it is possible that concurrent positive symptoms of psychosis in young adulthood are more related to social functioning than social functioning during the premorbid period in childhood and adolescence preceding psychosis. Due to the cross-sectional nature of these results, causal inferences cannot be made; however,

symptoms of psychosis seem to negatively influence social functioning in young adulthood in individuals with 22q11.2DS.

Specific Aim 3: Childhood Cognitive Predictors of Young Adult Social Functioning

Stability of social functioning. Childhood social functioning (Time 1) was a significant predictor of young adulthood social functioning (Time 4), when entered into the model as a covariate, for both the 22q11.2DS group and community controls. (No attempt was made to exclude ADHD, LD and intellectual delays from the community control group.) This suggests that social difficulties begin in childhood and these difficulties remain constant across a 9-year period. Our results are consistent with longitudinal studies in ASD (Howlin et al., 2013), suggesting stability of social difficulties across time. Similarly, our findings support previous 22q11.2DS studies suggesting that social difficulties are already present in middle childhood (elementary school) for children with 22q11.2DS (Campbell et al., 2011; Heineman-de Boer et al., 1999). It is possible that peer reputations developed when children begin school (middle childhood) are having a lasting impact on social functioning, a finding noted in typically developing populations (Bagwell et al., 1998; Morison & Masten, 1991). Children with 22q11.2DS are rejected by their peers in childhood (Campbell et al., 2011; Heineman-de Boer et al., 1999) and problems with interpersonal relationships, social leisure activities and coping with social experiences persist across time.

General intellectual abilities. Childhood full-scale IQ was not a significant predictor of young adult social functioning outcomes in all three groups. This did not support our hypothesis and suggests that global cognitive impairment does not predict social outcomes in individuals with 22q11.2DS. These findings differ from cross sectional studies conducted in 22q11.2DS in which general intelligence was associated with peer relationship problems in adolescence

(Campbell et al., 2015) and the VABS Socialization scale in adulthood (Butcher et al., 2012). General intelligence has also been identified as a correlate with social difficulties in a study with adolescents with Fragile X Syndrome (Turkstra et al., 2014). Our study was the first to examine this relationship longitudinally in 22q11.2DS. While it is possible that general intelligence impacts social functioning cross sectionally at various developmental time points (adolescence, adulthood) in 22q11.2DS, global cognitive impairments in childhood do not predict social functioning impairments in adulthood. The discrepancy between our findings and previous cross-sectional studies in 22q11.2DS (Butcher et al., 2012; Campbell et al., 2015) and Fragile X Syndrome (Turkstra et al., 2014) may be related to differences in measures used to examine these constructs. Another possible explanation is that when examining this relationship longitudinally, there are other childhood variables specific to 22q11.2DS (e.g., parent reported internalizing symptoms) that better explain social functioning difficulties later in life. A third possibility is that parents of youth with intellectual delays may have high expectations, a finding associated with youth accomplishments in multiple domains (Wagner & Sri International, 1993). In other words, parents of youth with 22q11.2DS continue to have high expectations for their child's social functioning despite their child's intellectual delays. Future longitudinal research should consider how parent expectations affect outcomes in 22q11.2DS.

Executive functions. Childhood executive functions (working memory, cognitive flexibility, response inhibition, and planning) did not longitudinally predict young adult social functioning in the 22q11.2DS and community control groups. These findings did not support our hypothesis and were inconsistent with previous cross-sectional 22q11.2DS studies (Campbell et al., 2015), longitudinal studies in ADHD (Diamantopoulou et al., 2007; Rinsky & Hinshaw, 2011) and schizophrenia (Sánchez et al., 2009) and cross-sectional studies in schizophrenia

(Rocca et al., 2009), ASD (Gilotty et al., 2002), Turner syndrome (Lepage et al., 2013) and Fragile x syndrome (Turkstra et al., 2014). Our results suggest that within 22q11.2DS, there are other childhood factors more related to social functioning difficulties in adulthood than executive functions. The lack of a significant longitudinal relationship between executive functions and social functioning outcomes may be related to differences in measures employed in our study compared to previous research; such as the memory task created by Campbell et al. (2015) in the study that found a cross-sectional relationship between working memory and social functioning in 22q11.2DS. Other possible explanations for these discrepancies include, the specificity of executive functioning problems as a function of the disorder examined, with some executive functioning deficits being more related to social abilities than others or the lack of statistical power in our community control group due to sample size. However, our results were consistent with cross-sectional studies in adults with schizophrenia (Addington et al., 1998) and ADHD (Biederman et al., 2004; Øie et al., 2011) that found no significant relationship between executive functions and social functioning. Rather than executive skills, within 22q11.2DS, social difficulties already present in childhood better explain social functioning outcomes in adulthood.

Planning is a significant predictor of self-reported social functioning in the sibling group, such that better planning abilities prospectively predicted higher social functioning. The functional consequences of this are unclear; however, Rinsky and Hinshaw (2011) also note similar findings in that planning abilities in childhood longitudinally predicted social functioning in girl adolescents with ADHD.

Specific Aim 4: Childhood Behavioral/Emotional Predictors of Adult Social Functioning

Childhood behavioral and emotional factors were also investigated as possible predictors

of young adult social functioning in all three groups. Internalizing symptoms are prevalent in 22q11.2DS (Jansen et al., 2007; Shashi et al., 2012; Stephenson, Beaton, Weems, Angkustsiri, & Simon, 2015; Wray, Shashi, Schoch, Curtiss, & Hooper, 2013). Our data suggest that not only are these symptoms common, parent reported internalizing symptoms in children with 22q11.2DS also predict parent reported poor social functioning in young adulthood. Even after controlling for the significant relationship between poor social functioning already present in childhood (time 1), parent reported elevated childhood internalizing symptoms explained problems with interpersonal relationships, social leisure activities and coping with social experiences in young adulthood. The model explained 46.1% of the variance in social functioning for the 22q11.2DS group. Given that this finding was only present within the 22q11.2DS group, the impact of childhood internalizing symptoms to social functioning outcomes may be more specific to 22q11.2DS.

We found that childhood internalizing symptoms (Time 1) were not related positive symptoms of psychosis in young adulthood (Time 4). These results differ from Gothelf et al. (2007) who indicated that anxiety and depression in childhood longitudinally predicted a schizophrenia diagnosis in adulthood. It is possible that negative symptoms of psychosis are more related to internalizing behaviors and when examining this relationship using only positive symptoms of psychosis this relationship is no longer present. Interestingly, even after controlling for psychosis, childhood internalizing symptoms still significantly explained poor social functioning in young adulthood. Overall, these variables explained 47.9% of the variance in social functioning for the 22q11.2DS group.

The link between internalizing symptoms and social functioning has been made in previous research in 22q11.2DS, such that internalizing symptoms and problematic social

behaviors that interfere with the ability to make and maintain friends in childhood were associated cross-sectionally (Shashi et al., 2012). Our study is the first to identify this relationship longitudinally. Butcher et al. (2012) did not find a significant association between a lifetime history of a mood/anxiety disorder diagnosis and social functioning in adults with 22q11.2DS. One simple explanation of these divergent results is that we measured internalizing symptoms dimensionally while Butcher et al. (2012) used a categorical approach.

It is also possible that this longitudinal relationship emerges because children with 22q11.2DS experience medical and emotional stressors early in life that may contribute to early experiences of anxiety, depression or somatization, and these symptoms influence later social functioning impairments. This is a well-documented finding in non-22q11.2DS research which has indicated that early symptoms of internalizing behaviors related to anxiety and depression in childhood have a negative impact on social outcomes in adolescence (Korhonen et al., 2014) and adulthood (Essau, Lewinsohn, Olaya, & Seeley, 2014; Maughan, Collishaw, & Stringaris, 2013). Internalizing symptoms have also been identified as related to functional outcomes (not specific to social functioning) in 22q11.2DS. In a cross-sectional sample, Angkustsiri et al. (2012) found higher symptoms of anxiety were related to lower adaptive functioning in children with 22q11.2DS. Likewise, in children with 22q11.2DS, a cross-sectional association was found between elevated symptoms of depression and poor adaptive functioning (Fabbro, Rizzi, Schneider, Debbane, & Eliez, 2012).

However, due to the relative variance for which childhood internalizing symptoms alone predict poor social functioning outcomes in young adulthood (15.3% of the variance) in the 22q11.2DS population, it is likely that there are other childhood factors explaining social functioning outcomes that have not yet been considered in 22q11.2DS. For example, constructs

specific to the clinical phenotype of individuals with 22q11.2DS, such as facial anomalies and speech and language delays (Shprintzen, 2000) may also be related to impairments in the ability to make and maintain friendships. Childhood bullying is also a well-documented predictor of poor social functioning outcomes in typically developing populations (Takizawa, Maughan, & Arseneault, 2014; Wolke, Copeland, Angold, & Costello, 2013). Bullying may be bi-directionally related to social functioning in 22q11.2DS, such that being bullied may lead to socially withdrawn behaviors or a lack of social opportunities with other children, which in turn interferes with the ability for individuals with 22q11.2DS to make and maintain friends. The opposite relationship is also likely, that because of social difficulties displayed in childhood, bullies may be targeting individuals with 22q11.2DS. Since we measured only one aspect of social cognition (emotion recognition), deficits in other domains of social cognition such as theory of mind may also explain poor social functioning outcomes in 22q11.2DS, a finding noted in schizophrenia literature (M. F. Green, Horan, & Lee, 2015). While there are likely other factors that explain adult social functioning, our data suggest that internalizing symptoms in childhood are clinically relevant and provide possible avenues for intervention.

Self-reported social skills were identified as a significant predictor of social functioning in the sibling group. This is consistent with findings in ASD literature (Gillespie-Lynch et al., 2012; Howlin et al., 2013). It is interesting that this finding did not emerge in the 22q11.2DS or community control groups, especially when one considers that social skills training interventions are one of the most widely used interventions to improve social outcomes. Our findings highlight the importance of treating internalizing symptoms in children with 22q11.2DS. This finding suggests that a potential research topic to explore would be the relative efficacy of social skill interventions that include treatment of internalizing symptoms versus those that only target social

skills.

Exploratory Aim 1: Child Behaviors Causing Parental Stress in Adolescence

We examined parent stress and family environment in adolescence as a possible mechanism for the impact of internalizing symptoms in childhood on social functioning outcomes in adulthood. Parents of the 22q11.2DS group reported higher child behavior problems that cause parental stress than both of the control groups and also higher total stress than the community control group. This is consistent with previous literature suggesting that parents of children with 22q11.2DS report three times higher stress levels compared to parents of typically developing children (Briegel et al., 2008). Stress experienced by parents has been linked to the frequency of problem behaviors displayed by children in previous 22q11.2DS studies (Briegel, Schneider, & Schwab, 2007; Briegel et al., 2008).

Our results indicated that parent reported child behavior problems in mid-adolescence contributing to parenting stress (Time 2) were a mediator of the relationship between childhood internalizing symptoms (Time 1) and parent-reported social functioning in young adulthood (Time 4). This suggests that child-related stresses exhibited through problem behaviors, including distractibility/hyperactivity, low adaptability, low acceptability, high demandingness, negative mood, and low ability to reinforce parents, are a mechanism by which internalizing behaviors may negatively impact social outcomes.

According to the transactional model, continuous reciprocal interactions between an individual and their environment are important to social development (Ollendick & Hirshfeld-Becker, 2002; Sameroff, 1995). Therefore, the interpersonal interactions between children with 22q11.2DS and their parents may contribute to the enduring effects of childhood internalizing symptoms and problematic behaviors in adolescence on social functioning later in life. While

much work remains to be done to understand these complex, transactional relationships, our results posit that when children with 22q11.2DS who experience anxious or depressive symptoms are presented with social opportunities, these children may exhibit behaviors to escape or avoid the social situations (e.g., crying to leave the room). These behaviors are distressing to parents and are possibly being negatively reinforced (e.g., removing the child from the situation). Negative reinforcement in turn may increase the frequency of problematic behaviors occurring across time (Derby et al., 1994). Parents who perceive their child as challenging may frequently respond negatively to the adolescent, and as a result continuously demonstrate poor social communication via modeling (McGuigan, Vuchinich, & Tang, 2014). Alternatively, these parents may limit social opportunities due to not typically receiving positive responses from their children in social situations (McLeod, Wood, & Weisz, 2007). These coercive parent-child interactions may continuously affect social functioning negatively over time and impact the social development of individuals with 22q11.2DS through adulthood.

It is possible that empirically based interventions for internalizing symptoms such as anxiety and depression will improve social outcomes in 22q11.2DS by teaching parents how best to respond to child problematic behaviors. For example, training parents in how to emphasize autonomy and reduce reliance upon parents is emphasized in some child anxiety treatment programs (Rapee, Wignall, Spence, Cobham, & Lyneham, 2008). Future studies should examine the extent to which internalizing symptom focused treatments such as the cognitive behavioral therapy (CBT) Coping Cat (Kendall & Hedtke, 2006) delivered in childhood can improve social functioning, both proximally in childhood and distally in adulthood (Beidas, Benjamin, Puleo, Edmunds, & Kendall, 2010). Due to cognitive impairments experienced by individuals with 22q11.2DS, it is quite likely that the CBT will need to be adapted (Fjermestad, Vatne, & Gjone,

2015).

Limitations

Results of the current study should be interpreted in the context of potential limitations. First, due to the discrepancy between parent-report and self-report measures of social functioning, it may be more valid to observe participants in their natural environment using a behavioral measure or sociometric surveys, to assess social functioning of participants with 22q11.2DS relative to their age matched peers. Second, we did not consider the possible influences of social skills training or any previous treatment that may impact social functioning (e.g., CBT, pharmacotherapy) on our results. It remains unknown how many individuals with 22q11.2DS received social skills training or other social functioning-based interventions before participating in the current study. Thus, before concluding that internalizing interventions are more likely than social skills training to have positive yields, future studies should control for the impact of social skills interventions. Third, while our 22q11.2DS analyses were adequately powered, the sample size of our other two groups is a limitation. Low statistical power may have increased our Type II error rates and hindered the ability for statistically significant effects to be detected in our sibling and community control groups. While these two control groups were not our primary focus, future studies should use larger sample sizes to increase statistical power. Also, we did not adjust alpha level when examining the relationship between the childhood variables and young adult social functioning because correcting for multiple comparisons may have masked true statistical significance and increased the likelihood of null findings, which would not have provided useful leads for future studies. However, future studies should consider correcting for alpha level to decrease the risk for Type 1 error within analyses.

Considering that there is no gold standard measure of social functioning, it is possible

that the VABS-II and the SAS-SR may be confounded by questions related to social skills. Future studies should be conducted comparing the construct validity of these measures with other instruments used in the literature to assess social functioning. Lastly, the current study did not manipulate variables and therefore one cannot assume causality between internalizing symptoms and social functioning. Experimental studies using randomized controlled designs should be used in future research to develop and test interventions designed to prevent/remediate social functioning impairments in 22q11.2DS.

Future Directions

Considering childhood social functioning explained social outcomes in adulthood in both individuals with 22q11.2DS and community controls, these findings suggest the need to consider interventions before school age (the children in our study were on average in middle childhood - 11 years of age - at the first time point). Future studies could examine variables in the preschool period which predict social functioning outcomes in middle childhood in order to develop interventions for both typically developing children and children with 22q11.2DS. In addition, the relatively stable social developmental trajectory for all groups in our study highlights the importance of screening for social functioning impairments at an early age across all individuals (yet especially in 22q11.2DS given their impairments) to intervene as early as possible.

Likewise, the relatively positive self-perception of individuals with 22q11.2DS that differed from parent-reports of social functioning raises the question of how best to intervene for children with 22q11.2DS. Future studies should consider using a parental psychoeducation intervention for parents of young adults with 22q11.2DS focused on appropriate social expectations given the developmental age of their children. Changing expectancies about their children's social development relative to other individuals with cognitive delays may motivate

parents to seek out developmentally appropriate social experiences for their children, in turn improving social functioning of individuals with 22q11.2DS. This line of intervention may be better suited than individual therapy for young adults with 22q11.2DS because due to the lack of social challenges reported by individuals with 22q11.2DS, a potential lack of motivation to change could negatively affect outcomes of interventions aimed at improving social functioning (Hoza & Pelham, 1995).

In addition, future research examining the relationship between childhood social functioning and the development of psychosis in 22q11.2DS is needed. More specifically, given that psychosis is associated with social functioning in young adulthood, investigating the utility of social functioning as an early detection indicator for psychosis risk remains an important line of future research (Lauronen et al., 2007). Lastly, considering the vast number of measures that have been used to assess social functioning, future studies are needed to compare instruments and examine the validity of commonly used measures. It remains difficult to compare results across studies with a variety of instruments being employed that may include items assessing different constructs (e.g., social skills). Identifying or creating a gold-standard instrument to measure social functioning would allow the field to move forward in making more methodologically sound conclusions.

Conclusions

In summary, using parent-reported social functioning as an outcome measure, the present study suggests parent reported symptoms of anxiety, depression, and somatization in childhood may have a long-term negative impact on social functioning in young adulthood, and may be mediated by the expression of problem behaviors that cause parental stress in adolescence. These results are important as social functioning was consistently rated as more impaired across

developmental periods (Time 1 to 4) for individuals with 22q11.2DS relative to their siblings and age matched peers. This highlights the need for intervention in early childhood in this vulnerable population and suggests that targeting internalizing symptoms and associated parental responses may be a viable research agenda to investigate.

Table 1

Longitudinal Predictors of Social Functioning in Disorders Associated with 22q11.2DS

Source	N	Length of longitudinal study	Ages throughout study	Clinical population	Childhood predictor of outcome	Measure of social functioning
Bongers et al. (2008)	2076	14 years	4-16 to 18-30 years old	Typically developing	Externalizing behaviors (opposition and status violations)	Groningen Questionnaire on Social Behaviour (GQSB)
Lauronen et al. (2007)	59	35 years	mid-gestation to 35 years old	Schizophrenia	Close friendships in childhood, age of psychosis onset	Social and Occupational Functioning Assessment Scale (SOFAS)
Sánchez et al. (2009)	95	6 months	18-65 years old	Schizophrenia	Executive functions (verbal memory, working memory)	World Health Organization Disability Assessment Schedule (WHO-DAS)
Rinsky and Hinshaw (2011)	140	5 years	6-12 to 11.3-18.2 years old	ADHD	Executive functions (planning, response inhibition)	Composite of: Dishion Social Preference Scale (DSPS), Social Skills Rating System (SSRS), Social Relationships Questionnaire (SRQ), Child Behavior Checklist (CBCL), Teacher Report Form (TRF)
Diamantopoulou et al. (2007)	112	1 year	8.5 to 9.5 years old	ADHD	Executive functions, ADHD symptoms	Peer nominations questionnaire
Øie, Sundet, and Ueland (2011)	19	12 years	12-18 to 24-30 years old	ADHD	No predictors found	Social Functioning Scale (SFS), Adult Self Report Scale (ASR), Global Assessment Scale of Function (GAS)
Gillespie-Lynch et al. (2012)	20	22 years (evaluated 4 times)	Mean ages at evaluations: Time 1: 3.9 years old Time 4: 26.6 years old	ASD	Language skills, responsiveness to joint attention	Vineland Adaptive Behavior Scales (VABS)
Howlin et al. (2013)	60	37 years	6.9 to 44.2 years old	ASD	Early symptoms of reciprocal interaction impairments, early language deficits	Family History Schedule (FHS)
Chromik et al. (2015)	73	8 years	6-18 to 15-26 years old	Fragile X Syndrome	ADHD symptoms	Vineland Adaptive Behavior Scales (VABS), Child Behavior Checklist (CBCL)

Table 2

Factors Associated with Social Functioning in Longitudinal and Cross-sectional Studies

Typically developing	Schizophrenia	ADHD	Anxiety	ASD	Genetic Disorders
Externalizing behaviors	Lack of close friends in childhood	Planning	Severity of disorder	Responsiveness to joint attention	Hyperactivity
Emotional Intelligence**	Early age of psychosis onset	Response inhibition*	Positive affect	Language skills	Executive function (composite)*
	Negative psychotic symptoms	Executive function (composite)*	Emotion regulation**	Reciprocal interaction	Working memory*
	Level of education	ADHD symptoms		Non-verbal IQ	Inhibitory control*
	Facial emotion recognition skills**			High level play	Non-verbal IQ
	Verbal memory			Executive function (composite)*	Comorbid diagnosis of ASD in DS
	Working memory*				
	Cognitive flexibility*				
	Theory of mind				

Note. *Executive functioning constructs were the most common factor associated with social functioning across disorders.
**Factors related to social cognition were commonly associated with social functioning across disorders.

Table 3

Sample Demographics

Variable	22q11.2DS (*n* = 53)	Siblings (*n* = 18)	Community Controls (*n* = 16)
Sex (% male)	52.8	50.0	68.8
T1 Age (years)	11.9 (2.1)	12.5 (2.0)	11.2 (1.6)
Range	8.9 to 16.0	9.2 to 15.8	8.5 to 15.8
T4 Age (years)	21.3 (2.2)	21.9 (1.8)	20.4 (1.5)
Range	18.1 to 25.9	19.0 to 24.5	18.9 to 24.7
Race (% percent)			
White	94.3	94.4	81.3
Asian	1.9	5.6	6.3
American Indian/Alaska Native	0		0
Black African American	0		0
More than one race	1.9		12.5
Unknown	1.9		
Ethnicity (% percent)			
Hispanic/Latino	3.8	5.6	0
Non-Hispanic/Latino	96.2	94.4	100.0

Table 4

Measures Used Across Time Points

Instrument	Time 1	Time 2	Time 3	Time 4
Social Adjustment Scale- Self-Report				x
Vineland Adaptive Behavior Scales, 2nd Edition	x			x
Wechsler Intelligence Scale for Children- 3rd edition	x			
Gordon Diagnostic System	x			
Wisconsin Card Sorting Test	x			
Stroop Color-Word Test	x			
California Verbal Learning Test-Children's version	x			
Visual Span Test	x			
Tower of London	x			
Penn Emotion Recognition- 40 Test	x			
Behavior Assessment System for Children- Parent Rating Scale	x			
Family Environment Scale- 4th Edition		x		
Parenting Stress Index- 3rd Edition		x		

Table 5

Correlation Coefficients for 22q11.2DS

	r																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1. Full Scale IQ	1																				
2. Freedom from Distractibility	.75**	1																			
3. Verbal IQ	.94**	.73**	1																		
4. GDS Commission	.13	.25	.05	1																	
5. WCST Perseverative	.20	.36**	.13	.38**	1																
6. WCST Non-Perseverative	.47**	.45**	.39**	.15	.48**	1															
7. Stroop Interference	.21	.41*	.13	.29	.31	.42*	1														
8. CVLT-C List A Trial 1	.30*	.25	.24	-.04	.01	.28	.20	1													
9. CVLT-C List A Trial 5	.49**	.45**	.40**	.10	.35*	.39**	-.12	.42**	1												
10. CVLT-C List B	.42**	.35*	.41**	-.05	.08	.37**	-.13	.31*	.45**	1											
11. Visual Span Forward	.35*	.39**	.30*	.35*	.25	.43**	.22	.17	.21	.21	1										
12. Visual Span Backward	.45**	.37**	.41**	-.04	.02	.25	-.03	.22	.35**	.36**	.36**	1									
13. Tower of London	-.26	-.27	-.14	-.26	-.19	-.17	-.53**	-.04	.04	-.12	-.07	-.03	1								
14. Time 1 VABS-II Socialization	.50**	.45**	.53**	-.00	.33*	.41**	-.11	.08	.31*	.44**	.31*	.28*	-.14	1							
15. Time 4 VABS-II Socialization	.20	.23	.30*	-.09	.21	.03	-.14	-.14	.01	.16	.07	.07	.15	.58**	1						
16. SAS_SR	-.27	-.14	-.26	.29*	.07	-.05	.29	.05	-.04	.00	-.05	-.25	-.02	-.48**	-.44**	1					
17. BASC Internalizing	-.11	-.22	-.27	.05	.05	.00	.05	.06	.19	-.14	-.09	-.19	-.21	-.30*	-.53**	.24	1				
18. BASC Externalizing	-.14	-.14	-.22	-.18	-.12	.02	.11	-.01	.12	-.22	-.33*	-.06	.08	-.44**	-.41**	.04	.44**	1			
19. BASC Social Skills	.29*	.25	.36*	-.19	.19	.14	-.08	.01	.10	.39**	.04	.21	-.05	.63**	.42**	-.36*	-.41**	-.37**	1		
20. Emotion Recognition	.39**	.56**	.32*	.03	.30*	.29*	.36*	.08	.31*	.15	.07	.17	-.42**	.36*	.06	-.26	.01	.04	.13	1	
21. SIPS Positive Symptoms	-.02	-.07	-.06	.23	-.03	.07	-.08	.32*	.12	-.04	.23	.12	.10	-.13	-.37**	-.41**	.20	-.04	-.08	-.28*	1

Note. GDS = Gordon Diagnostic System, WCST = Wisconsin Card Sorting Test, Stroop = The Stroop Color-Word Test, CVLT-C = California Verbal Learning Test-Children's version, VABS-II = Vineland Adaptive Behavior Scales - Second Edition, SAS-SR = Social Adjustment Scale – Self-Report, BASC-PRS = Behavior Assessment System for Children- Parent Rating Scale, SIPS = Structured Interview for Prodromal Symptoms (SIPS) * $p < .05$, ** $p < .01$.

Table 6

Correlation Coefficients for Siblings

		r																		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1.	Full Scale IQ	1																			
2.	Freedom from Distractibility	.73**	1																		
3.	Verbal IQ	.94**	.80**	1																	
4.	GDS Commission	.45	.52*	.48*	1																
5.	WCST Perseverative	.57*	.57*	.59**	.49*	1															
6.	WCST Non-Perseverative	.56*	.42	.61**	.37	.81**	1														
7.	Stroop Interference	.30	.04	.22	.30	.08	.12	1													
8.	CVLT-C List A Trial 1	.67**	.50*	.73**	.34	.57*	.66**	.51	1												
9.	CVLT-C List A Trial 5	.56*	.50*	.56*	.54*	.45	.71**	.32	.67**	1											
10.	CVLT-C List B	.38	.62**	.54*	.47*	.48*	.35	-.06	.42	.31	1										
11.	Visual Span Forward	.27	.31	.31	.31	-.07	.02	.24	.34	.44	-.08	1									
12.	Visual Span Backward	.45	.55*	.44	.59*	.45	.33	-.26	.35	.48*	.26	.41	1								
13.	Tower of London	-.63**	-.57*	-.62**	-.66**	-.50*	-.39	-.31	-.52*	-.45	-.39	-.04	-.46	1							
14.	Time 1 VABS-II Socialization	.22	.22	.45	-.04	.22	.37	-.25	.24	.09	-.04	.30	.25	.02	1						
15.	Time 4 VABS-II Socialization	.27	.16	.30	.08	.46	.58*	.04	.42	.36	-.07	.08	.47	-.15	.43	1					
16.	SAS_SR	.00	-.12	.04	-.06	-.33	-.05	-.10	.12	.22	-.02	.41	.04	.44	-.01	-.06	1				
17.	BASC Internalizing	-.22	-.26	-.25	-.18	.01	-.02	-.18	-.46	-.47	.09	-.55*	-.34	.06	-.09	-.09	-.48	1			
18.	BASC Externalizing	-.62**	-.63**	-.76**	-.04	-.41	-.61**	.12	-.42	-.46	-.33	-.21	-.24	.05	-.65**	-.42	-.05	.09	1		
19.	BASC Social Skills	.30	.26	.46	.06	.31	.66**	-.26	.37	.44	.08	.32	.23	.24	.71**	.36	.41	-.17	-.76**	1	
20.	Emotion Recognition	.54*	.52*	.58*	.26	.69**	.47*	-.25	.38	.12	.29	.16	.53*	-.46	.48	.36	-.36	.22	-.35	.22	1

Note. GDS = Gordon Diagnostic System, WCST = Wisconsin Card Sorting Test, Stroop = The Stroop Color-Word Test, CVLT-C = California Verbal Learning Test-Children's version, VABS-II = Vineland Adaptive Behavior Scales - Second Edition, SAS-SR = Social Adjustment Scale – Self-Report, BASC-PRS = Behavior Assessment System for Children- Parent Rating Scale

* $p < .05$, ** $p < .01$.

Table 7

Correlation Coefficients for Community Controls

	r																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1. Full Scale IQ	1																			
2. Freedom from Distractibility	.78**	1																		
3. Verbal IQ	.91**	.70**	1																	
4. GDS Commission	.23	.33	.19	1																
5. WCST Perseverative	.35	.36	.28	.23	1															
6. WCST Non-Perseverative	.22	.26	.11	.16	.89**	1														
7. Stroop Interference	.52	.58*	.56*	.08	.03	.07	1													
8. CVLT-C List A Trial 1	.02	.04	.04	.10	.01	-.07	.39	1												
9. CVLT-C List A Trial 5	.41	.45	.33	.38	.15	.06	.35	.44	1											
10. CVLT-C List B	.11	.13	.14	.06	.08	-.22	.07	.09	.53*	1										
11. Visual Span Forward	.62*	.57*	.46	.14	.49	.38	.26	-.26	.35	.24	1									
12. Visual Span Backward	.49	.62*	.46	.04	.29	.06	.57*	.13	.30	.34	.53*	1								
13. Tower of London	-.23	-.32	-.27	-.59*	.08	.00	-.14	.01	-.47	.13	-.32	-.01	1							
14. Time 1 VABS-II Socialization	.40	.50*	.50*	.27	.35	.10	.19	.29	.25	.18	.02	.55*	-.10	1						
15. Time 4 VABS-II Socialization	.38	.56*	.33	-.24	.27	.03	.12	-.01	.07	.18	.32	.74**	.22	.61*	1					
16. SAS_SR	-.17	-.35	-.04	-.56*	-.21	.04	.04	-.24	-.29	-.02	-.21	-.33	.24	-.38	-.42	1				
17. BASC Internalizing	-.39	-.21	-.58*	.12	-.07	.04	-.17	.15	-.03	-.23	-.10	-.09	.07	-.42	-.18	-.35	1			
18. BASC Externalizing	-.05	-.18	-.05	-.14	.25	.14	.03	-.02	-.35	-.22	.33	.41	.07	.05	.20	-.17	.16	1		
19. BASC Social Skills	-.11	.14	-.08	.27	.30	.37	-.21	.35	.04	-.21	-.32	-.20	-.08	.46	.04	-.09	-.10	-.33	1	
20. Emotion Recognition	.66**	.31	.68**	.02	.51*	.22	.14	.08	-.03	.08	.40	.42	.14	.55*	.40	-.16	-.42	.44	-.03	1

Note. GDS = Gordon Diagnostic System, WCST = Wisconsin Card Sorting Test, Stroop = The Stroop Color-Word Test, CVLT-C = California Verbal Learning Test-Children's version, VABS-II = Vineland Adaptive Behavior Scales - Second Edition, SAS-SR = Social Adjustment Scale – Self-Report, BASC-PRS = Behavior Assessment System for Children- Parent Rating Scale

* $p < .05$, ** $p < .01$.

Table 8

Social Functioning Outcome Variables

Variable	22q11.2DS (*n* = 53)	Siblings (*n* = 18)	Community Controls (*n* = 16)	Significant main effects
T1 VABS-II Socialization Standard score	72.2 (20.6)***	98.9 (20.6)	95.3 (13.4)	22q11.2DS < sibling, control
T2 VABS-II Socialization Standard score	72.1 (18.8)***	97.6 (17.3)	95.1 (17.9)	22q11.2DS < sibling, control
T3 VABS-II Socialization Standard score	71.3 (10.9)***	97.3 (12.7)	97.0 (13.6)	22q11.2DS < sibling, control
T4 VABS-II Socialization Standard score	68.9 (13.4)***	95.8 (12.8)	94.9 (15.9)	22q11.2DS < sibling, control
T4 SAS-SR Social and Leisure Activities T-score	58.2 (10.4)	52.1 (11.0)	56.8 (8.1)	None
T4 SAS-SR Work Domain T-score	59.3 (15.7)	57.1 (11.6)	52.9 (9.0)	None
T4 SAS-SR Relationships with Extended Family T-score	63.5 (15.9)	60.8 (12.6)	54.6 (12.2)	None
T4 SAS-SR Role as a spouse or partner T-score	53.0 (19.8) *n* = 2	49.6 (8.4) *n* = 5	53.5 (23.3) *n* = 2	None
T4 SAS-SR Parental role T-score	N/A	43.5 (5.0) *n* = 2	N/A	
T4 SAS-SR Role within the family unit T-score	60.7 (24.1)	50.4 (10.1)	50.1 (16.9)	None

Note. VABS-II = Vineland Adaptive Behavior Scales - Second Edition, SAS-SR = Social Adjustment Scale – Self-Report
* P < 0.05. ** P < 0.01, *** P < 0.001.

Table 9

Time 1 Cognitive Variable Means

Variable	22q11.2DS (*n* = 53)	Siblings (*n* = 18)	Community Controls (*n* = 16)	Significant main effects
WISC-III Full Scale IQ Standard score	69.6 (12.5)***	102.7 (16.3)	98.3 (12.7)	22q11.2DS < sibling, control
WISC-III Freedom From Distractibility Index Standard score	78.7 (13.2)***	100.4 (13.3)	93.3 (13.4)	22q11.2DS < sibling, control
WISC-III Verbal IQ Standard score	73.1 (13.6)***	100.4 (14.5)	96.5 (13.6)	22q11.2DS < sibling, control
GDS Commission Errors z-score	-2.9 (5.0)*	0.0 (1.2)	-2.2 (2.7)	22q11.2DS < sibling
TOL Total moves Raw score	136.0 (35.6)*	105.6 (20.1)	116.3 (22.3)	22q11.2DS > sibling
WCST Perseverative Errors Standard score	71.4 (15.5)***	94.7 (16.5)	95.9 (17.1)	22q11.2DS < sibling, control
WCST Non-perseverative errors Standard score	82.3 (15.1)	89.2 (16.0)	91.8 (16.2)	None
Stroop Interference Score T-score	47.0 (9.8)	53.8 (12.2)	46.8 (7.4)	None
CVLT-C List A Trial 1 Score z-score	-0.9 (1.0)**	-0.1 (1.0)	-0.2 (0.6)	22q11.2DS < sibling, control
CVLT-C List A Trial 5 Score z-score	-1.1 (1.3)**	0.3 (1.2)	0.0 (0.8)	22q11.2DS < sibling, control
CVLT-C List B Score z-score	-0.7 (1.1)	-0.4 (0.8)	-0.3 (0.8)	None
Visual Span Test Forward Span z-score	-0.9 (0.6)***	0.4 (0.6)	-0.2 (0.8)	22q11.2DS < sibling, control
Visual Span Test Backward Span z-score	-1.3 (1.0)***	-0.1 (1.0)	-0.5 (1.3)	22q11.2DS < sibling, control

Note. WISC-III = Wechsler Intelligence Scale for Children- 3rd edition, GDS = Gordon Diagnostic System, TOL = The Tower of London, WCST = Wisconsin Card Sorting Test, Stroop = The Stroop Color-Word Test, CVLT-C = California Verbal Learning Test-Children's version
* P < 0.05. ** P < 0.01, *** P < 0.001.

Table 10

General Intelligence Predicting Parent-reported Social Functioning 22q11.2DS

Variable		β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1				.554	.307	.294	.000*	
	Time 1 Vineland Socialization	.554	4.76				.000*	1.00
Step 2				.558	.312	.284	.569	
	Time 1 Vineland Socialization	.590	4.43				.000*	1.29
	FSIQ	-.076	-.573				.569	1.29

Note. FSIQ = Full Scale IQ
* P < 0.05.

Table 11

General Intelligence Predicting Parent-reported Social Functioning in Siblings

Variable		β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1				.427	.182	.131	.077	
	Time 1 Vineland Socialization	.427	1.89				.077	1.00
Step 2				.468	.219	.115	.414	
	Time 1 Vineland Socialization	.389	1.67				.116	1.04
	FSIQ	.196	.84				.414	1.04

Note. FSIQ = Full Scale IQ
* $P < 0.05$.

Table 12

General Intelligence Predicting Parent-reported Social Functioning in Community Controls

Variable		β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1				.605	.366	.321	.013*	
	Time 1 Vineland Socialization	.605	2.85				.013*	1.00
Step 2				.623	.388	.294	.505	
	Time 1 Vineland Socialization	.541	2.29				.039*	1.19
	FSIQ	.162	.69				.505	1.19

Note. FSIQ = Full Scale IQ
* $P < 0.05$.

Table 13

Cognitive Predictors of Parent-reported Social Functioning in 22q11.2DS

Variable		β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1				.554	.307	.307	.000*	
	Time 1 Vineland Socialization	.554	4.76				.000*	1.00
Step 2				.555	.308	.001	.794	
	Time 1 Vineland Socialization	.537	3.98				.000*	1.32
	WISC-III Verbal IQ	.035	.26				.794	1.32
Step 3				.640	.410	.102	.112	
	Time 1 Vineland Socialization	.604	4.37				.000*	1.49
	WISC-III Verbal IQ	.206	1.36				.180	1.78
	Working Memory Composite	-.293	-1.92				.062	1.83
	Response Inhibition Composite	.000	.001				1.00	1.18
	Cognitive Flexibility Composite	.031	.218				.829	1.59
	Planning score	.237	2.01				.050	1.09

Note. WISC-III = Wechsler Intelligence Scale for Children- 3rd edition
* $P < 0.05$.

Table 14

Cognitive Predictors of Self-reported Social Functioning in 22q11.2DS

Variable		β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1				.166	.028	.028	.235	
	WISC-III Verbal IQ	-.166	-1.20				.235	1.00
Step 2				.339	.115	.088	.339	
	WISC-III Verbal IQ	-.239	-1.36				.179	1.64
	Working Memory Composite	.129	.70				.485	1.80
	Response Inhibition Composite	.292	1.98				.054	1.16
	Cognitive Flexibility Composite	-.049	-.29				.771	1.48
	Planning score	.028	.19				.847	1.09

Note. WISC-III = Wechsler Intelligence Scale for Children- 3rd edition
* $P < 0.05$.

Table 15

Cognitive Predictors of Parent-reported Social Functioning in Siblings

Variable		β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1				.427	.182	.182	.077	
	Time 1 Vineland Socialization	.427	1.89				.077	1.00
Step 2				.451	.203	.021	.542	
	Time 1 Vineland Socialization	.368	1.48				.160	1.17
	WISC-III Verbal IQ	.156	.63				.542	1.17
Step 3				.615	.378	.175	.563	
	Time 1 Vineland Socialization	.357	.36				.245	1.49
	WISC-III Verbal IQ	-.392	-.39				.423	3.93
	Working Memory Composite	.425	.43				.336	3.16
	Response Inhibition Composite	-.310	-.31				.411	2.33
	Cognitive Flexibility Composite	.464	.46				.216	2.20
	Planning score	-.097	-.10				.786	2.17

Note. WISC-III = Wechsler Intelligence Scale for Children- 3rd edition
* $P < 0.05$.

Table 16

Cognitive Predictors of Self-reported Social Functioning in Siblings

Variable		β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1				.041	.002	.002	.871	
	WISC-III Verbal IQ	.041	.17				.871	1.00
Step 2				.731	.534	.533	.043*	
	WISC-III Verbal IQ	.375	1.04				.321	3.39
	Working Memory Composite	.473	1.35				.202	3.16
	Response Inhibition Composite	.311	1.09				.298	2.10
	Cognitive Flexibility Composite	-.477	-1.65				.126	2.17
	Planning score	.881	3.10				.009*	2.08

Note. WISC-III = Wechsler Intelligence Scale for Children- 3rd edition
* $P < 0.05$.

Table 17

Cognitive Predictors of Parent-reported Social Functioning in Community Controls

Variable		β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1				.605	.366	.366	.013*	
	Time 1 Vineland Socialization	.605	2.85				.013*	1.00
Step 2				.606	.367	.001	.919	
	Time 1 Vineland Socialization	.592	2.32				.037*	1.34
	WISC-III Verbal IQ	.027	.10				.919	1.34
Step 3				.839	.703	.336	.112	
	Time 1 Vineland Socialization	.578	2.55				.031*	1.56
	WISC-III Verbal IQ	-.031	-.13				.902	1.77
	Working Memory Composite	.508	2.14				.062	1.72
	Response Inhibition Composite	-.484	-1.8				.104	2.18
	Cognitive Flexibility Composite	.050	.21				.837	1.71
	Planning score	.157	.68				.511	1.59

Note. WISC-III = Wechsler Intelligence Scale for Children- 3rd edition
* $P < 0.05$.

Table 18

Cognitive Predictors of Self-reported Social Functioning in Community Controls

Variable		β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1				.035	.001	.001	.899	
	WISC-III Verbal IQ	-.035	-.13				.899	1.00
Step 2				.621	.386	.385	.257	
	WISC-III Verbal IQ	.336	1.07				.310	1.61
	Working Memory Composite	-.428	-1.35				.206	1.63
	Response Inhibition Composite	-.591	-1.67				.126	2.04
	Cognitive Flexibility Composite	.253	.78				.452	1.71
	Planning score	-.071	-.23				.822	1.54

Note. WISC-III = Wechsler Intelligence Scale for Children- 3rd edition
* P < 0.05.

Table 19

Time 1 Emotional and Behavioral Variable Means

Variable	22q11.2DS (*n* = 53)	Siblings (*n* = 18)	Community Controls (*n* = 16)	Significant main effects
Penn Emotion Recognition Test Raw Score	31.6 (7.2)***	38.3 (2.0)	37.0 (3.9)	22q11.2DS < sibling, control
BASC-PRS Externalizing Composite T-score	55.4 (12.3)*	47.7 (8.0)	47.3 (8.9)	22q11.2DS > control
BASC-PRS Internalizing Composite T-score	60.3 (15.2)***	43.9 (5.4)	50.1 (9.3)	22q11.2DS > sibling, control
BASC-PRS Social Skills T-score	40.7 (9.7)***	51.7 (10.4)	52.3 (8.5)	22q11.2DS < sibling, control

Note. BASC-PRS = The Behavior Assessment System for Children-Parent Rating Scale
* P < 0.05. ** P < 0.01, *** P < 0.001.

Table 20

Emotional/Behavioral Predictors of Parent-reported Social Functioning in 22q11.2DS

Variable		β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1				.554	.307	.307	.000*	
	Time 1 Vineland Socialization	.554	4.76				.000*	1.00
Step 2				.555	.308	.001	.794	
	Time 1 Vineland Socialization	.537	3.98				.000*	1.32
	WISC-III Verbal IQ	.035	.26				.794	1.32
Step 3				.679	.461	.153	.019*	
	Time 1 Vineland Socialization	.499	3.09				.003*	2.23
	WISC-III Verbal IQ	.001	.01				.991	1.39
	BASC-PRS Internalizing Behaviors	-.381	-2.99				.005*	1.39
	BASC-PRS Externalizing Behaviors	-.047	-.36				.717	1.44
	BASC-PRS Social Skills	-.064	-.44				.666	1.82
	Penn ER-40	-.099	-.82				.417	1.24

Note. Penn ER-40 = Penn Emotion Recognition- 40 Test, BASC-PRS = Behavior Assessment System for Children- Parent Rating Scale
* $P < 0.05$.

Table 21

Emotional/Behavioral Predictors of Self-reported Social Functioning in 22q11.2DS

Variable	β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1			.166	.028	.028	.235	
WISC-III Verbal IQ	-.166	-1.20				.235	1.00
Step 2			.348	.121	.093	.304	
WISC-III Verbal IQ	-.029	-.19				.849	1.26
BASC-PRS Internalizing Behaviors	.084	.52				.605	1.38
BASC-PRS Externalizing Behaviors	-.095	-.60				.549	1.32
BASC-PRS Social Skills	-.264	-1.65				.106	1.37
Penn ER-40	-.151	-1.04				.303	1.13

Note. Penn ER-40 = Penn Emotion Recognition- 40 Test, BASC-PRS = Behavior Assessment System for Children- Parent Rating Scale
* $P < 0.05$.

Table 22

Emotional/Behavioral Predictors of Parent-reported Social Functioning in Siblings

Variable		β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1				.427	.182	.182	.077	
	Time 1 Vineland Socialization	.427	1.89				.077	1.00
Step 2				.451	.203	.021	.542	
	Time 1 Vineland Socialization	.368	1.48				.160	1.17
	WISC-III Verbal IQ	.156	.63				.542	1.17
Step 3				.513	.263	.060	.919	
	Time 1 Vineland Socialization	.125	.29				.780	2.84
	WISC-III Verbal IQ	-.181	-.40				.697	3.07
	BASC-PRS Internalizing Behaviors	-.156	-.51				.622	1.41
	BASC-PRS Externalizing Behaviors	-.343	-.67				.518	3.93
	BASC-PRS Social Skills	-.024	-.05				.958	3.06
	Penn ER-40	.327	.81				.437	2.45

Note. Penn ER-40 = Penn Emotion Recognition- 40 Test, BASC-PRS = Behavior Assessment System for Children- Parent Rating Scale
*P < 0.05.

Table 23

Emotional/Behavioral Predictors of Self-reported Social Functioning in Siblings

Variable	β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1			.041	.002	.002	.871	
WISC-III Verbal IQ	.041	.17				.871	1.00
Step 2			.770	.593	.591	.021*	
WISC-III Verbal IQ	.396	1.28				.225	2.82
BASC-PRS Internalizing Behaviors	-.210	-.98				.347	1.35
BASC-PRS Externalizing Behaviors	.673	1.92				.078	3.60
BASC-PRS Social Skills	.829	2.84				.015*	2.51
Penn ER-40	-.489	-1.95				.075	1.86

Note. Penn ER-40 = Penn Emotion Recognition- 40 Test, BASC-PRS = Behavior Assessment System for Children- Parent Rating Scale
*P < 0.05.

Table 24

Emotional/Behavioral Predictors of Parent-reported Social Functioning in Community Controls

Variable		β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1				.605	.366	.366	.013*	
	Time 1 Vineland Socialization	.605	2.85				.013*	1.00
Step 2				.606	.367	.001	.919	
	Time 1 Vineland Socialization	.592	2.32				.037*	1.34
	WISC-III Verbal IQ	.027	.10				.919	1.34
Step 3				.674	.455	.088	.830	
	Time 1 Vineland Socialization	.819	2.14				.061	2.43
	WISC-III Verbal IQ	-.043	-.10				.926	3.43
	BASC-PRS Internalizing Behaviors	.100	.32				.759	1.64
	BASC-PRS Externalizing Behaviors	.040	.11				.917	2.33
	BASC-PRS Social Skills	-.316	-.92				.383	1.97
	Penn ER-40	-.012	-.03				.980	3.84

Note. Penn ER-40 = Penn Emotion Recognition- 40 Test, BASC-PRS = Behavior Assessment System for Children- Parent Rating Scale
* $P < 0.05$.

Table 25

Emotional/Behavioral Predictors of Self-reported Social Functioning in Community Controls

Variable	β	t	R	R^2	ΔR^2	Sig.	VIF
Step 1			.035	.001	.001	.899	
WISC-III Verbal IQ	-.035	-.13				.899	1.00
Step 2			.520	.271	.270	.488	
WISC-III Verbal IQ	-.233	-.49				.638	3.16
BASC-PRS Internalizing Behaviors	-.590	-1.72				.117	1.62
BASC-PRS Externalizing Behaviors	-.037	-.09				.929	2.28
BASC-PRS Social Skills	-.188	-.62				.553	1.29
Penn ER-40	-.236	-.45				.659	3.71

Note. Penn ER-40 = Penn Emotion Recognition- 40 Test, BASC-PRS = Behavior Assessment System for Children- Parent Rating Scale
*P < 0.05.

Table 26

Time 2 Variables used for Mediation Model Means

Variable	22q11.2DS (*n* = 53)	Siblings (*n* = 18)	Community Controls (*n* = 16)	Significant main effects
Time 2 FES Cohesion Standard score	52.4 (16.9)	54.1 (16.3)	59.2 (6.6)	None
Time 2 FES Expressiveness Standard score	53.2 (12.7)	53.6 (15.1)	57.0 (12.2)	None
Time 2 FES Conflict Standard score	47.5 (12.2)	48.4 (14.4)	42.8 (9.7)	None
Time 2 PSI Total Parent Stress Standard score	238.0 (39.6)**	208.3 (43.3)	195.2 (35.2)	22q11.2DS > control
Time 2 PSI Parent Domain Standard score	109.9 (22.0)	113.3 (26.9)	102.8 (17.8)	None
Time 2 PSI Child Domain Standard score	127.2 (23.3)***	94.7 (18.8)	92.5 (22.1)	22q11.2DS > sibling, control

Note. FES = Family Environment Scale-4th Edition, PSI = Parenting Stress Index-3rd Edition
* P < 0.05. ** P < 0.01, *** P < 0.001.

Table 27

PSI Child Domain Mediates Time 1 Internalizing Behaviors and Time 4 Social Functioning

	X	Y	Beta weight	t	R	R^2	Sig.
Path a							
	T1 BASC Internalizing Behaviors	T2 PSI Child Domain	.633	2.79	.416	.173	.008*
Path b							
	T2 PSI Child Domain	T4 VABS-II Socialization	-.173	-2.00	.623	.388	.053
Path c’							
	T1 BASC Internalizing Behaviors	T4 VABS-II Socialization	-.408	-3.11	.623	.388	.004*
Indirect Effect							
	T1 BASC Internalizing Behaviors	T4 VABS-II Socialization	-.408	LL CI = -.3705		UU CI = -.0048	
	T2 PSI Child Domain						

Note. T1 = Time 1, T2 = Time 2, T4 = Time 4, VABS-II = Vineland Adaptive Behavior Scales, Parent- Report, PSI = Parenting Stress Index-3rd Edition, BASC-PRS = Behavior Assessment System for Children- Parent Rating Scale

Figure 1

Social Functioning Outcome Variables Between Groups

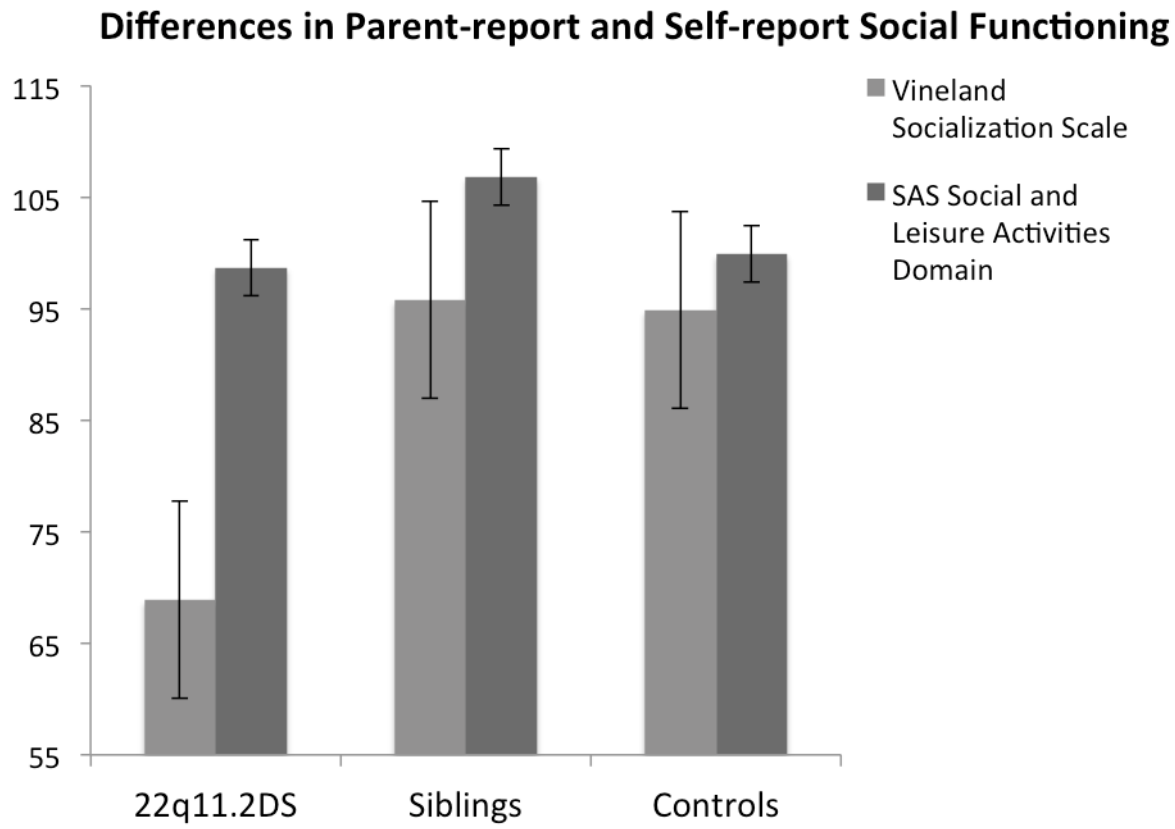


Figure 2

Vineland Socialization Scale Across Time

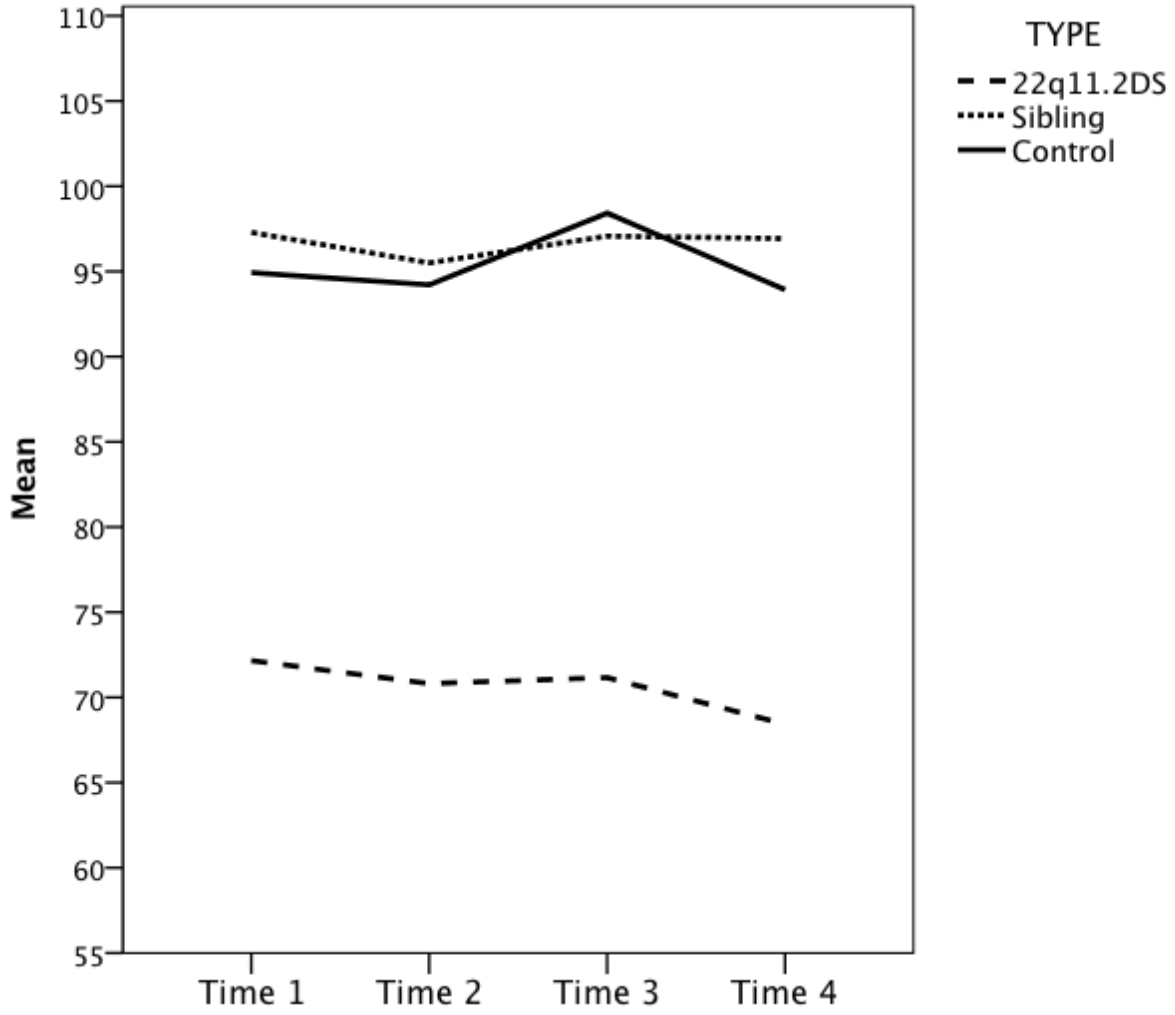


Figure 3

Instruments and Scores used to Measure Executive Functions

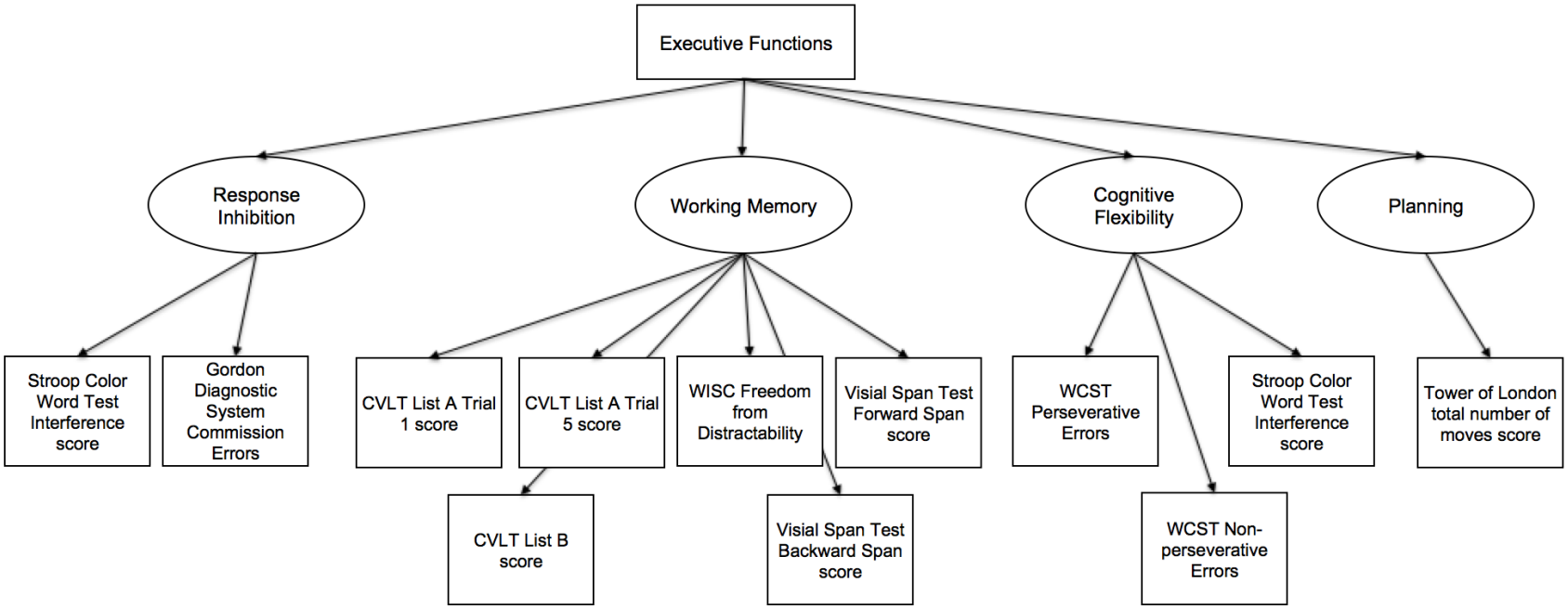
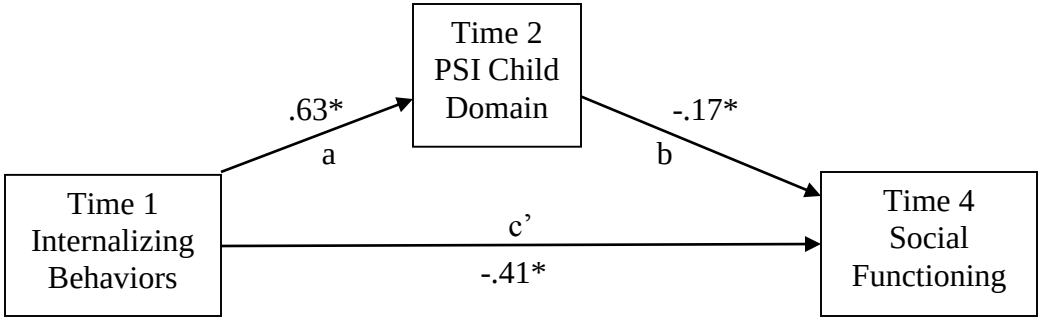


Figure 4

Mediation model for Childhood Internalizing Behaviors on Young Adult Parent-reported Social Functioning: (1) Total Effect (c) and (2) Direct Effect (c') and Indirect Effect (ab)



Indirect Effect = (ab) = -0.11*

Note. *Significant at the 0.05 level

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