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Childhood Predictors of Young Adult Social Functioning in 22q11.2 Deletion Syndrome

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Abstract

Background—The primary objectives of the current prospective longitudinal study were to (a) describe social functioning outcomes and (b) identify childhood predictors of social functioning in young adults with 22q11.2 Deletion Syndrome (22q11.2DS).

Method—Childhood predictors of young adult social functioning were examined. Family environment and parental stress in adolescence were investigated as potential mediators between childhood variables and adult social functioning.

Results—Parent rated childhood internalizing symptoms significantly predicted young adult social functioning in 22q11.2DS, even after controlling for concurrent positive symptoms of psychosis, and problem behaviors contributing to parenting stress in adolescence partially mediated this relationship.

Conclusions—These findings highlight child internalizing symptoms and adolescent problem behaviors as potential targets for social functioning interventions in 22q11.2DS.

Keywords

social functioning; 22q11.2 Deletion Syndrome (22q11.2DS); developmental delay; internalizing; longitudinal

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Compliance with Ethical Standards

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Conflict of Interest: The authors declare they have no conflicts of interest.

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22q11.2 deletion syndrome (22q11.2DS) is 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 1,000–5,950 live births (Botto et al., 2003; Grati et al., 2015). 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 0.3 – 0.7% 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, visual/spatial memory, attention and executive functions are areas of relative weakness (Antshel et al., 2008).

Executive Functions

Executive functions are an area of both relative and normative weakness for individuals with 22q11.2DS (Antshel et al., 2008). 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) (Miyake et al., 2000; Pennington & Ozonoff, 1996). These components of executive functioning (working memory, behavioral inhibition, cognitive flexibility, and planning) are necessary for effective social interactions (Altgassen & Kliegel, 2014; 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). Social functioning domains can 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). In contrast, social skills 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). Simply having the social skills does not guarantee that the skills will be deployed or lead to successful social relationships.

Social functioning is an important construct to study, yet has received scant attention by 22q11.2DS researchers. This is unfortunate as peer rejection or low acceptance among peers in childhood is related to a wide variety of negative outcomes, both concurrently and prospectively (Bagwell, Newcomb, & Bukowski, 1998; Boivin, Hymel, & Bukowski, 1995; Hodges, Malone, & Perry, 1997; Ladd, Kochenderfer, & Coleman, 1996; Parker & Asher, 1987). More specific to 22q11.2DS, given that poor social functioning in childhood is a predictor of psychosis in adulthood (Lauronen et al., 2007; Yuen, Chow, Silversides, & Bassett, 2013) and individuals with 22q11.2DS are at an increased risk for schizophrenia (Drew et al., 2011), social functioning seems an especially important variable to investigate in the 22q11.2DS 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 early elementary school 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. Three cross-sectional research studies, however, have examined this research question. In each study, cognitive variables (executive functioning, intelligence) or internalizing behaviors were identified as being associated with social functioning. For example, parents of 24 adolescents with 22q11.2DS reported their children experiencing significantly more peer relationship problems compared to parent reports of 27 age-matched typically developing peers (Campbell et al. 2015). In the 22q11.2DS group, (a) working memory, (b) general intelligence, and (c) the ability to understand the emotions of others (emotion attribution) were each negatively associated with peer relationship problems.

Likewise, a cross-sectional study of 100 adults with 22q11.2DS also reported social functioning impairments in adults with 22q11.2DS (Butcher et al., 2012). In this study, a significant positive association between the full-scale IQ and social functioning outcomes was reported. A schizophrenia diagnosis was also a significant predictor of lower social functioning in this cross-sectional sample. Finally, in a cross-sectional study, Shashi et al. (2012) demonstrated that internalizing behaviors are associated with social functioning problems in children with 22q11.2DS.

Although these 3 cross sectional research studies in 22q11.2DS are 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.

Current Study Specific Aims / Hypotheses

This project investigates a clinically significant and novel research topic that has clear implications for intervention development and potentially prevention in 22q11.2DS. 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), prevention efforts could potentially be 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.

Considering that no previous studies 22q11.2DS included both self and parent reports, we include both in our study. Likewise, we included both siblings and community controls as comparison groups to (a) examine differences in social development, (b) control for environmental effects (e.g., socioeconomic status, home environment, etc.) 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. Our four specific aims and associated hypotheses 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 (Butcher et al., 2012; Campbell et al., 2015) and working memory (Campbell et al., 2015) was previously noted to be associated with social outcomes in 22q11.2DS cross-sectional studies. In the non-22q11.2DS literature, executive functioning skills including response inhibition, cognitive flexibility, working memory and planning have been documented to be associated with social functioning (Diamantopoulou, Rydell, Thorell, & Bohlin, 2007; Gilotty, Kenworthy, Sirian, Black, & Wagner, 2002; Lepage, Dunkin, Hong, & Reiss, 2013; Rinsky & Hinshaw, 2011; Rocca et al., 2009; Sánchez et al., 2009; Turkstra, Abbeduto, & Meulenbroek, 2014). Accordingly, 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, are associated with social functioning (Extremera & Fernández-Berrocal, 2006). In 22q11.2DS, internalizing behaviors are associated with social functioning (Shashi et al., 2012). In the non- 22q11.2DS literature, both internalizing behaviors (Jacob, Suveg, & Whitehead, 2014; Settipani & Kendall, 2013) and externalizing behaviors (Bongers et al., 2008; Chromik et al., 2015; Diamantopoulou et al., 2007) are associated with social funcitoning. Thus, we hypothesize that childhood emotion recognition, internalizing behaviors and externalizing behaviors will significantly predict young adult social functioning in all three groups.

Exploratory aim 1. For any significant childhood predictors in Specific Aim 3 or 4, we will explore adolescent family environment and parental stress as mediators of the relationship between any significant childhood variables and young adult social functioning in the 22q11.2DS group.

Parents/primary caregivers of youth with 22q11.2DS report three times higher stress levels compared to parents of typically developing children (Briegel, Schneider, & Schwab, 2008). Moreover, non-22q11.2DS research suggests that parental stress is significantly associated with the frequency of problem behaviors displayed by their children (Plant & Sanders, 2007), and negatively predicts the quality of peer-based social interactions in children with developmental delays (Guralnick, Hammond, Connor, & Neville, 2006). Accordingly, we will explore whether parental stress mediates the relationship between childhood variables and social functioning outcomes in young adulthood.

Parents of children with 22q11.2DS also 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). Moreover, family environment can influence social functioning (e.g., modeling how to resolve conflicts) in typically developing adolescents (Youngblade et al., 2007). Accordingly, we will also explore whether family environment mediates the relationship between childhood factors and young adult social functioning in individuals with 22q11.2DS.

Method

Participants

Recruitment—This study consists of a subsample of individuals who participated in a 9-year longitudinal study of risk factors for psychosis in 22q11.2DS. The current sample consists of 53 children with 22q11.2DS, 18 age and gender matched siblings of children with 22q11.2DS and 16 community controls (CC) who were each assessed at four time points (every three years). 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 22q11.2DS Center at BLINDED FOR REVIEW. 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 instructed in a general education classroom.

Demographics—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. As shown in Table 1, 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, $p = .661$.

Attrition—When comparing our study sample (i.e., participants who had both Time 1 and Time 4 data) 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, gender, and socioeconomic status ($p > .05$) or any relevant social and cognitive measures, including Time 1 Vineland Socialization scores, Time 1 FSIQ, and Time 1 Verbal IQ ($p > .05$). Thus, the participants in the current study appear to be representative of the larger study sample.

Young Adult Dependent Measures

Table 2 presents the timeline of when each measure was administered. Participants were assessed at four different time points; however, information from time 3 is not used in the current study.

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 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. For the present study, the standard score of Social and Leisure Domain was used as a self-report measure of social functioning, with higher scores indicating more social impairment. 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.”

Vineland Adaptive Behavior Scales, Second Edition (Sparrow et al., 2005)— The Vineland Adaptive Behavior Scales- 2nd edition (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). For the present study, only the standard score of the Socialization scale was used as a parent-report of social adaptive functioning, with higher scores indicating better functioning. Low to moderate associations were noted between parent- and self-report of social functioning (22q11.2DS $r = -.44$, siblings $r = -.06$, and community controls $r = -.42$) indicating that they are measuring somewhat different constructs.

Young Adult Predictor Measure

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. 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. Higher scores on the SIPS indicate the presence of more positive symptoms of psychosis.

Childhood Cognitive Predictors

Wechsler Intelligence Scale for Children- 3rd edition (Wechsler, 1991)—The Wechsler Intelligence Scale for Children-3rd edition (WISC-III) FSIQ and Verbal IQ were used to assess general intellectual functioning and language abilities respectively. 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 (Mayes & Calhoun, 2006; Wechsler, 1991).

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. For the present study, only the standardized commission errors score were used in the analyses.

Tower of London (Shallice, 1982)—The Tower of London (TOL) has demonstrated good construct validity as a measure of planning (Culbertson & Zillmer, 1998). The total number of moves was used in analyses.

Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993)— The Wisconsin Card Sorting Test (WCST) is a task that measures cognitive flexibility. We used the standard scores for perseverative errors and non-perseverative errors in our analyses.

Stroop Color-Word Test (Golden, 1978)—The Stroop Color-Word Test is a task that measures cognitive flexibility, selective attention and response inhibition. The interference T-score was used in the present study.

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. 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 in analyses.

Visual Span Test (Davis, 1998)—The Visual Span Test is a computer-based test that assesses visual working memory abilities. The forward and backward span standardized z-scores were used in the current study.

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. Total number of correct responses was used as a measure of emotion recognition in the current study. 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. For the present study, based upon our a priori hypotheses, only the Externalizing composite score, Internalizing composite score, and the Social Skills subscale score were used.

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. For the current study, standard scores on the FES relationship domain subscales (Cohesion, Expressiveness, Conflict) were used, with higher scores indicating higher parent reported emphasis on that construct within the family.

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 Child Domain, Parent Domain, and Total Parent Stress composite scores were used as our parenting stress variables.

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

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) (Costa, 2014; Tabachnick & Fidell, 2007). 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 (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 (Raaijmakers, 1999).

Specific aim 1—A one-way analysis of variance (ANOVA) was used to assess if mean differences existed in social functioning for individuals with 22q11.2DS, siblings and controls in young adulthood. A one-way ANOVA was also 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) was used to examine the mean differences in social functioning between groups while controlling for full-scale IQ. Tukey post-hoc tests identified the groups with significant mean differences. Homogeneity of variance was tested using Levene's Test for Equality of Variances for between subject comparisons.

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. A correlation coefficient of *.80* was used as a cutoff (Tabachnick & Fidell, 2007). In addition, multicollinearity diagnostics were also conducted for every regression analysis using variance inflation factor (VIF). 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 and kurtosis of Time 4 social functioning was evaluated. Using the criteria of West, Finch, and Curran (1995) all variables were normally distributed.

Specific aim 2—Specific aim 2 was examined in the 22q11.2DS group only. Zero-Inflated Poisson (ZIP) regression analyses (Lambert, 1992) were conducted using the SIPS Positive Symptoms Score to assess the relationship between Time 4 positive symptoms of psychosis and our Time 4 social functioning measures, the VABS-II Socialization and SAS-SR. A Vuong test 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—A multiple linear regression analysis was conducted separately for each study group to determine if childhood general intelligence (Specific Aim 3a) or childhood executive functioning abilities (Specific Aim 3b) predicted young adult social functioning.

Executive functioning composite scores: As noted in Figure 1, multiple instruments were used to assess response inhibition, cognitive flexibility, and working memory. To reduce the chance of Type I errors, composite scores for each of these 3 subdomains were created by averaging z-scores for each test variable. 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. 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). Since we only used the Tower of London scores to assess planning, however, an average z-score was not created for this domain.

Covariates: VABS scores at time 1 were entered as a covariate in regression models predicting to parent reported–social functioning (VABS-II) outcomes in adulthood, to account for the potential effects of childhood social functioning. We did not covary for time 1 self-reported social functioning in regression models predicting to Time 4 SAS-SR Social and Leisure Activities scores since we did not collect a self-reported measure of social functioning at Time 1.

Since language skills are related to social functioning (Gillespie-Lynch et al., 2012; Howlin, Moss, Savage, & Rutter, 2013; Liss et al., 2001), Verbal IQ was also entered into the model to account for the variance verbal abilities may have on an individual's ability to make or maintain relationships with others.

Specific aim 4—Multiple linear regression analyses were conducted separately for each study group to determine if young adult social functioning could be predicted from childhood behavioral functioning or emotion recognition constructs. We again entered social functioning at Time 1 and Verbal IQ as covariates to account for the variance that childhood social functioning and verbal abilities may have on social functioning outcomes in young adulthood, in order to identify what other behavioral/emotional variables may be contributing to parent reported social functioning.

Exploratory aim 1—Based on the significant childhood predictors of young adult social functioning that emerged from analyses in Specific Aims 3 and 4, mediation analyses were conducted to examine if adolescent (Time 2) family environment or parental stress mediated the relationship. To test the proposed indirect effect 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 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.

Statistical power—Before conducting our analyses, we ran a power analysis using our cognitive regression model with the most variables (Specific Aim 3), an effect size of 0.25 and alpha as 0.05 in G power. Results indicated that our sample size (53 participants) is adequate to achieve .80 statistical power in 22q11.2DS, yet not in the other two groups.

Results

Specific Aim 1

Young adult social functioning group differences—There was a statistically significant difference in the parent-reported VABS-II Socialization scale at Time 4, $F(2,84) = 38.2$, $p < 0.001$. Tukey post-hoc tests suggest that parents of participants with 22q11.2DS reported significantly lower social functioning than both the sibling and CC groups. The siblings and CC groups did not differ from each other (See Figure 2).

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, $F(2,134) = 57.6$, $p < 0.001$. Likewise, there was still a group effect 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 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 ($p > .05$). 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 parent-reported VABS-II Socialization scale and the self-report 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 ($p > .05$).

Finally, a repeated measures ANOVA was conducted to examine the effect of time on the parent-reported VABS-II Socialization scale. The interaction between time and group failed to reach statistical significance, $F(6, 204) = .339$, $p = .898$ (See Figure 3). There was also no significant effect of time on the parent reports of social functioning, $F(3, 204) = .671$, $p = .553$. Thus, parent reported socialization ratings were relatively constant across time in all three groups.

Specific Aim 2

Psychosis and social functioning—The ZIP regression conducted for the 22q11.2DS group that examined the association between Time 4 parent-reported VABS-II Socialization ratings and 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 were associated with 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 3, univariate results showed significantly lower performance for the 22q11.2DS group than both the sibling group and CC group for most cognitive variables.

Specific Aim 3a - Regression analyses of childhood general intelligence— Linear regression analyses examining the relationships between FSIQ 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 parent-reported VABS-II 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 4 for 22q11.2DS results.

In the sibling group, step 1 (Time 1 parent-reported VABS-II Socialization) was non-significant and the model remained non-significant in Step 2 (FSIQ) $p > .05$. Lastly, in the CC group, the majority of the variance explained was accounted for in step 1 (Time 1 parent-reported VABS-II 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 VABS-II Socialization. Thus, in all 3 groups, childhood FSIQ did not predict young adult social functioning after controlling for Time 1 social functioning.

When Time 4 VABS-II Socialization was used as the outcome variable, but Time 1 social functioning was not included as a covariate, the models for child FSIQ predicting young adult social functioning in 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 parent-reported socialization scale of the VABS-II for the 22q11.2DS ($r = .20$), sibling ($r = .27$) or community control ($r = .38$) groups.

When the self-reported SAS-SR social and leisure activities domain was used as the outcome variable, the FSIQ models described above were non-significant for all three groups ($p > .05$).

Specific Aim 3b - Executive functioning composite variables

22q11.2DS group executive functioning: In the 22q11.2DS group, when using the Time 4 parent-reported VABS-II Socialization Scale as the outcome variable, the majority of the variance explained was accounted for in step 1 (Time 1 VABS-II 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 VABS-II Socialization ($p > .05$). 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 ($p > .05$) (See Table 4).

Sibling group executive functioning: In the sibling group, when using Time 4 parent reported VABS-II Socialization as the outcome variable, step 1 (Time 1 VABS-II Socialization), step 2 (Verbal IQ) and step 3 (Executive Function mean z-score scores) were each not significant ($p > .05$) The regression analysis for siblings including the self-reported 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 self-reported SAS-SR social and leisure activities ($\beta = .88$, $p = .009$).

Community control group executive functioning: In the CC group, when using Time 4 parent-reported VABS-II Socialization as the outcome variable, the majority of the variance explained was accounted for in step 1 (Time 1 VABS-II 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 VABS-II Socialization ($p > .05$). 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 ($p > .05$)

Specific Aim 4

Childhood behavioral / emotional variable group differences—A MANOVA was conducted using childhood behavioral and emotional predictors. There was a significant multivariate effect ($F(8,150) = 5.07$, $p < .001$; Wilk's $\lambda = 0.590$, partial $\eta^2 = .23$). As shown in Table 5, 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 $\eta^2 = .20$), 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 $\eta^2 = .25$), 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 parent-reported VABS-II Socialization as the outcome variable, the majority of the

variance explained was accounted for in step 1 (Time 1 VABS-II 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 VABS-II Socialization. The overall model accounted for 46.1% of the variance in Time 4 VABS-II Socialization. Of the behavioral/ emotional variables included, only BASC internalizing behaviors ($\beta = -.38$, $p = .005$) significantly predicted young adult social functioning in 22q11.2DS (See Table 6).

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 ($p > .05$).

Follow up analyses: Since a significant relationship was previously demonstrated between Time 4 SIPS Positive symptoms and Time 4 VABS-II Socialization (Specific Aim 2), and Time 1 BASC internalizing symptoms seem to be making a significant contribution to Time 4 VABS-II 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 were 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 VABS-II Socialization Scale as the outcome variable, step 1 was significant (Time 1 VABS-II 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 VABS-II 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 young adult social functioning in the 22q11.2DS group.

Sibling group behavioral/emotional models: In the sibling group, when using the Time 4 parent-reported VABS-II Socialization Scale as the outcome variable, neither step 1 (Time 1 VABS-II Socialization), step 2 (Verbal IQ) nor step 3 (Time 1 Behavioral and Emotional scores) predicted Time 4 parent-ratings ($p > .05$). When the self-reported 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).

Community control group behavioral/emotional models: In the CC group, when using Time 4 parent-reported VABS-II Socialization Scale as the outcome variable, the majority of the variance explained was accounted for in step 1 (Time 1 VABS-II 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 VABS-II Socialization (p > .05). When the self-reported SAS-SR social and leisure activities domain was used as the outcome measure, neither step 1 (Verbal IQ) nor step 2 (Time 1 Behavioral and Emotional scores) were significant (p > .05).

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 for this variable.

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 7, univariate results showed significantly higher scores for the 22q11.2DS group than the CC group, but not the sibling group on PSI Total Parent Stress score (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 score (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 score 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 parent-reported young adult social functioning (Time 4 VABS-II Socialization scale). The indirect effect was tested using a bootstrap estimation approach with 1000 samples.

Results showed that parent reported BASC internalizing behaviors were a significant predictor of the PSI child score (β = .63, SE = .23, p = .008) and that the PSI child score 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) (See 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 self-reported SAS-SR social and leisure activities domain as the outcome variable.

Discussion

The present study is, to our knowledge, 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 social difficulties in 22q11.2DS in young adulthood. High parenting stress from problematic behaviors displayed by adolescents with 22q11.2DS mediated the relationship between elevated internalizing symptoms in childhood and lower 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 as having more difficulty with interpersonal relationships, seeking out social activities, and demonstrating proper coping skills in social settings during all developmental periods. Our results are also similar to those reported by Butcher et al. (2012), with both studies reporting that parent reported social functioning in young adults with 22q11.2DS is greater than 2 standard deviations below the mean (< 1st percentile).

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 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), which has been forwarded as a hypothesis to explain the commonly noted positive self-perceptions that exist in individuals with 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 is specific to 22q11.2DS. 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 in 22q11.2DS, both cross-sectionally (Yuen et al., 2013) and, in our sample, longitudinally (Radoeva, Fremont, Antshel, & Kates, 2016).

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

Stability of social functioning—Childhood social functioning was a significant predictor of young adulthood social functioning, when entered into the model as a covariate, for both the 22q11.2DS group and community controls. 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 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 elementary 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 these problems with interpersonal relationships, social leisure activities and coping with social experiences appear to persist across time.

Unlike the community control and 22q11.2DS groups, childhood social functioning was not a significant predictor of young adult social functioning in siblings. One possible explanation for this finding may be statistical and related to a restricted range of scores in the sibling group. A second possible explanation for this lack of an association between childhood and young adult social functioning relates to having a sibling with 22q11.2DS and the great variability that exists in psychiatric functioning in youth with 22q11.2DS. Via changes in psychiatric functioning in the proband with 22q11.2DS, the sibling's social development may be less consistent across time. Future research should continue to explore how best to understand our finding that childhood social functioning was not a significant predictor of young adult social functioning in siblings

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). 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 young adulthood. The discrepancy between our findings and previous cross-sectional studies in 22q11.2DS (Butcher et al., 2012; Campbell et al., 2015) 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.

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). Unlike the non-significant 22q11.2DS and community control findings, childhood planning abilities was a significant predictor of self-reported social functioning in the sibling group; better planning abilities prospectively predicted higher social functioning. This finding is consistent with those reported by Rinsky and Hinshaw (2011). In their study, planning abilities in childhood longitudinally predicted social functioning in girl adolescents with ADHD. Future research should continue to explore why these predicted associations were not observed in the 22q11.2DS and community control groups.

Our results suggest that within 22q11.2DS, there are other childhood factors that better predict 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. 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. 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.

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

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 poor social functioning already present in childhood, 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 to 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. Previous work from our group suggested that a composite comprised of parent reported child symptoms of anxiety, depression, somatization, withdrawal and atypicality on the BASC predicted to late adolescent psychosis (Kates et al., 2014). The present results differ, possibly due to (a) the different follow-up periods (late adolescence in previous work, young adulthood in current work) and (b) the inclusion of withdrawal and atypicality symptoms, which may be driving the relationship with psychosis. Future research should continue to investigate how best to predict psychosis in the 22q11.2DS population.

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 possible 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 (again, not specific to social 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. 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 (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.

Parent-reported social skills did not predict adult social functioning in the 22q11.2DS or community control groups. This is interesting, especially when one considers that social skills training interventions are a widely used intervention 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 interventions that include treatment of internalizing symptoms versus those that only target social skills.

Exploratory Aim 1: Child Behaviors Causing Parental Stress in Adolescence

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 take this line of research a step further and indicate 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 such as child distractibility/hyperactivity, low adaptability, low acceptability, high demandingness, negative mood, and low ability to reinforce parents, may be 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. It is possible that evidence based interventions for internalizing symptoms 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 interventions. Third, while our 22q11.2DS analyses were adequately powered and the 22q11.2DS analyses were our primary interest, 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. 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. Lastly, while 22q11.2DS can be readily identifiable by facial features, due to the genetic risk in 22q11.2DS, future studies should consider the use of genetic testing to confirm the absence of a genetic disorder in sibling samples.

Conclusions

In summary, 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.

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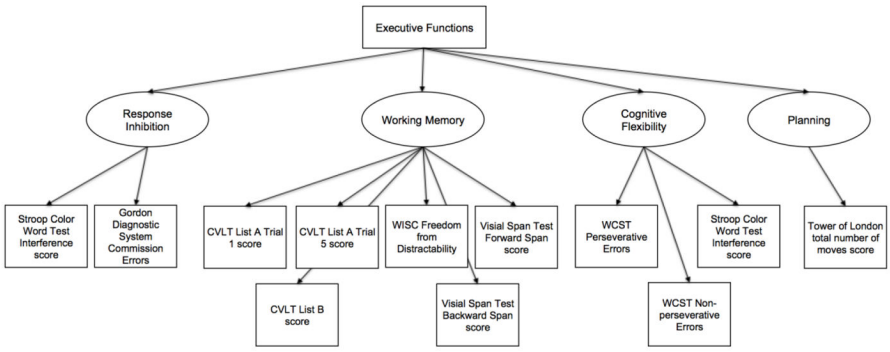

Figure 1.
Instruments used to Measure Executive Functions

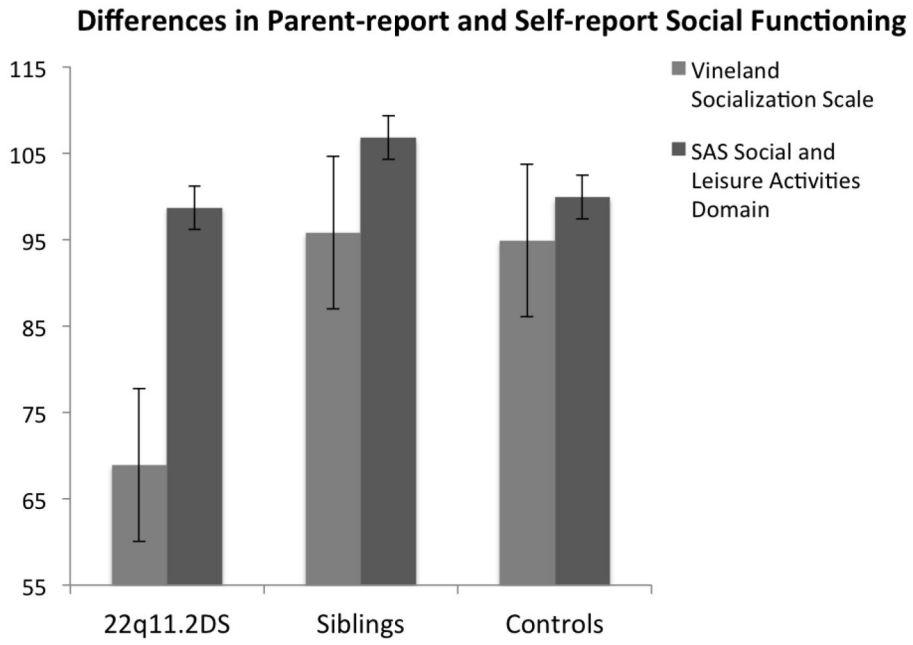

Figure 2.
Social Functioning Outcome Variables Between Groups

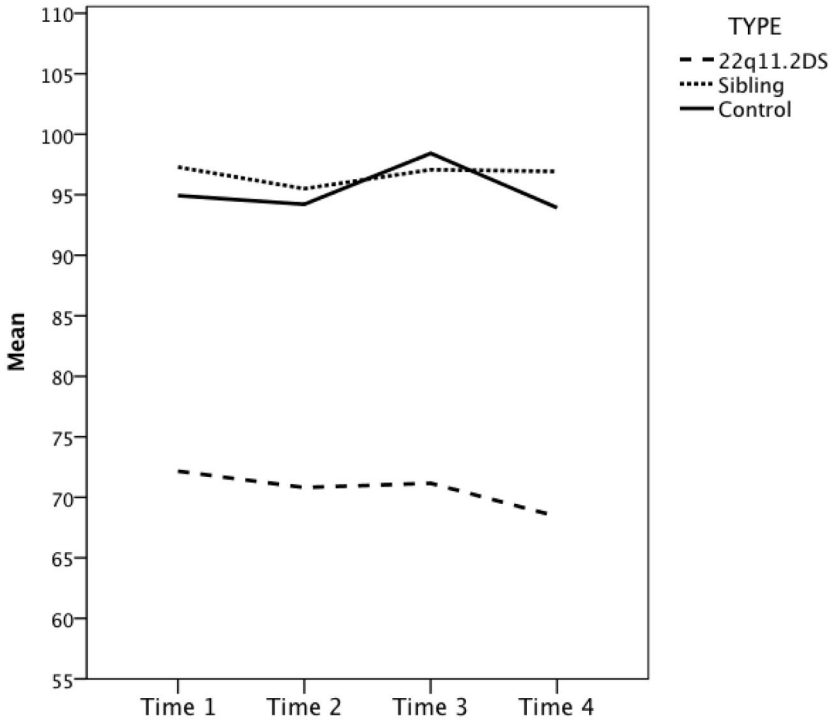

Figure 3.
Vineland Socialization Scale Across Time

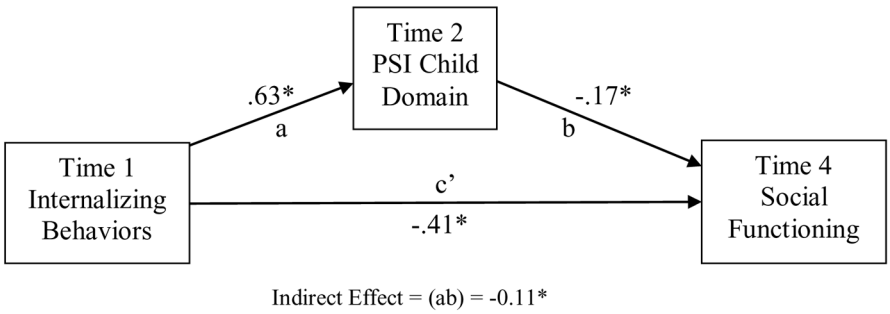

Figure 4.

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)

Note. *Significant at the 0.05 level

Table 1

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 2

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 (VABS-II)	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 3

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 4

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

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. FSIQ = Full Scale IQ. VIF = Variance Inflation Factor.

Table 5

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 < 0.001.

Table 6

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 7

Adolescent 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 < 0.01,

*** P < 0.001.