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Stephenson, DD
Beaton, EA
Weems, CF
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Research report

Identifying patterns of anxiety and depression in children with chromosome 22q11.2 deletion syndrome: Comorbidity predicts behavioral difficulties and impaired functional communications

David D. Stephenson[a], Elliott A. Beaton[a,b,c,*,1], Carl F. Weems[a], Kathleen Angkustsiri[c,d], Tony J. Simon[b,c,**]

[a] Department of Psychology, University of New Orleans, 2000 Lakeshore Dr., New Orleans, LA 70148, United States
[b] Department of Psychiatry and Behavioral Sciences, University of California Davis, 2230 Stockton Bvld., Sacramento, CA 95817, United States
[c] MIND Institute, University of California Davis, 2825 50th Street, Sacramento, CA 95817, United States
[d] Department of Pediatrics, 2516 Stockton Blvd., Sacramento, CA 95817, United States

HIGHLIGHTS

- Chromosome 22q11.2 deletion syndrome (22qDS) conveys a very high risk for psychosis.
- Children with high anxiety and co-morbid depression may be most vulnerable.
- Cluster analyses reduced sample heterogeneity to find highest risk profiles.
- Most children had higher anxiety but no depression but some were comorbid.
- Comorbidity predicted impaired communication and reduced daily life activities.

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ABSTRACT

Background: Chromosome 22q11.2 deletion syndrome (22q11.2DS) is a complex genetic disorder with a variable clinical presentation that can include cardiac, neural, immunological, and psychological issues. Previous studies have measured elevated anxiety and depression in children with 22q11.2DS. Comorbity of anxiety and depression is well established in the pediatric literature but the nature of comorbidity patterns has not been empirically established in children with 22q11.2DS. Comorbidity of anxiety and depression has important implications for treatment and prognosis, and may be a marker of risk in this population of children at high-risk for developing schizophrenia.
Method: Participants were 131 boys and girls ages 8–14 with ($n = 76$) and without ($n = 55$) 22q11.2DS and their mothers. Children and mothers independently completed self- and parent-report measures of anxiety and depression. Mothers also completed measures of behavioral functioning including the Behavioral Assessment for Children, 2nd ed. (BASC-2). Cluster analyses were conducted to test if theoretically based groupings of anxiety and depression could be identified. We hypothesized four psychological profiles based on child- and mother-reports: low/no anxiety and low/no depression, higher depression and low/no anxiety, higher anxiety and no/low depression, and a comorbid profile of higher anxiety and higher depression. BASC-2 subscale scores were then compared across subgroups of children to determine if a comorbid profile would predict greater behavioral difficulties.

Abbreviations: 22q11.2DS, chromosome 22q11.2 deletion syndrome; ADHD, attention deficit hyperactivity disorder; ANOVA, analysis of variance; ANCOVA, analysis of covariance; BASC-2, Behavior Assessment for Children 2nd Edition; BIC, Bayesian information criterion; CDI, Children's Depression Inventory; FSIQ, full scale intelligence quotient; IQ, intelligence quotient; MANOVA, multivariate analysis of variance; MASC, Multidimensional Anxiety Scale for Children; ms, milliseconds; PRI, perceptual reasoning index; TD, typically developing; VCFS, velocardiofacial syndrome; VCI, verbal comprehension index; UCD, University of California Davis; UNO, University of New Orleans.

* Corresponding author at: Department of Psychology, University of New Orleans, 2000 Lakeshore Dr., New Orleans, LA 70148, United States. Tel.: +1 504 280 6763; fax: +1 504 280 6049.
** Corresponding author at: MIND Institute, University of California Davis, 2825 50th Street, Sacramento, CA 95817, United States. Tel.: +1 916 703 0407; fax: +1 916 703 0244.
E-mail addresses: ebeaton@uno.edu (E.A. Beaton), tjsimon@ucdavis.edu (T.J. Simon).
[1] Now at the University of New Orleans.

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Results: In the full sample of children both with and without 22q11.2DS, cluster analyses of self and maternal reported anxiety and depression revealed the expected subgroups: (1) a group of children with higher anxiety/lower depression (anxious); (2) a group with primary depression (lower anxiety/higher depression (depressed)); (3) a comorbid group with higher anxiety/higher depression (comorbid); and, (4) a lowest anxiety/lowest depression group (NP). Mothers' reports produced highly similar groupings. Furthermore, the 22q11.2DS youth were more likely to be in anxiety, depressed or comorbid clusters than the typically developing (TD) youth. Children with 22q11.2DS comorbid for anxiety and depression exhibited the worst functional outcomes (e.g., poor poorer functional communication, and reduced daily life activities).
Conclusions: Anxiety, comorbid with depression may be of particular concern in children with 22q11.2DS who arguably carry a greater burden on their stress coping resources than children without a complex genetic disorder. Furthermore, the manifestation of negative mood, anxiety and difficult behavior is likely to reverberate between the child and her or his environment. This can lead to negative interactions with family, peers, and teachers, which in turn further taxes coping resources. Comorbidity of anxiety and depression within a vulnerable population highlights the need for the development of tailored interventions.

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1. Background

Chromosome 22q11.2 deletion syndrome (22q11.2DS), previously known as velocardiofacial or DiGeorge syndrome, is a complex and highly variable neurodevelopmental disorder with a prevalence between 1:2000 and 1:4000 live births [1]. Developmental impairments are evident in infancy and extend into adulthood. Early medical concerns can be serious and include cardiac malformations, atypical brain development, metabolic disorders and immunological issues [2–4]. As the child with 22q11.2DS grows, intellectual and cognitive impairments [5], combined with delayed socioemotional development [6,7] may arise from and also contribute to behavioral and psychiatric problems [8]. Of particular note, 22q11.2DS confers a 25–30 fold increased risk of schizophrenia or psychotic depression in adulthood compared to the general population [9] with over 40 percent of young and mature adults meeting diagnostic criteria for any schizophrenia spectrum disorder in a pooled sample of 1402 children and adults with 22q11.2DS [1]. The origin of this risk and potential interventions are a focus of intensive investigation by a variety of research groups. A variety of factors that appear to moderate likelihood of developing schizophrenia have been reported with elevated anxiety and mood as common factors. Anxiety and mood disorders are common in children and adolescents with 22q11.2DS [1,10–12]. Debbané et al. [13] found that 28 percent of a sample of 43 children and adolescents with 22q11.2DS exhibited psychotic symptoms. In their sample, lower verbal intelligence, poorer adaptive skills and a withdrawn, anxious-depressed affective profile predicted psychotic symptomology. Angkustsiri and colleagues [14] reported that elevated anxiety, rather than global intelligence, predicts poorer adaptive function in children with 22q11.2DS highlighting the impact of anxiety on daily functioning and experiential-mediated development. Gothelf and colleagues [15] also found anxiety and depression in children with 22q11.2DS to be predictive of psychosis in later life.

Comorbidity of mood and anxiety can predict poorer treatment outcomes in typically developing (TD) children [16,17] but this is not inevitable [18]. Treatment can be complicated by the addition of behavioral disorders such as attention deficit hyperactivity disorder (ADHD) [19,20], with ADHD being the most common diagnosis in children with 22q11.2DS [1,21]. Comorbidity of anxiety and depression is particularly likely in older children, especially those with a medical condition [22,23]. Other studies have found varying profiles of anxiety and depression in those with Down syndrome [24], autism spectrum disorder [25], and ADHD [26]. A child with 22q11.2DS arguably faces more medical, social and emotional stressors over time with poorer coping resources than his or her typically developing peers [27] and this may contribute to elevated anxiety and depression with cognitive, emotional, and behavioral impairments that can further contribute to anxiety and depression in a feed-forward fashion [28].

In the largest collaborative data analyses to date of a pooled sample of 1402 children and adults with 22q11.2DS, the presence of an anxiety disorder was positively associated with having a mood disorder. Furthermore, the presence of an anxiety disorder was positively associated with comorbidity of a mood and schizophrenia spectrum disorder. Comparably, the presence of a mood disorder in participants from this large pooled sample was positively predictive of comorbid anxiety and a schizophrenia spectrum disorder [1]. Risk indicators for the development of psychosis in children with 22q11.2DS appear to have a common theme of anxiety and mood disorder comorbidity. Comorbidity could arise along several developmental pathways including a diathesis for anxiety with depression developing from anxiety-related impairments, a diathesis for depression with anxiety developing from depression-related impairments, or possibly a diathesis for anxiety and depression that develop at the same time [28]. Anxiety and mood disorders appear to be a recurring theme affecting immediate quality of life but also the etiopathology of psychosis through adolescence and adulthood in children with 22q11.2DS. Thus, careful characterization of anxiety, depression, and comorbidity is an important step in characterizing the schizophrenia endophenotype in this population.

The first aim of the present study was to use cluster analyses to determine if distinct subgroups based on anxiety and depression symptomology were evident in a sample of children (ages 7–14) with 22q11.2DS and TD controls. The second aim was to determine if apparent subgroups differed in terms of behavioral and functional problems. Based on the multiple pathways model of anxiety and depression comorbidity [28], we hypothesized that there would be four subgroups within the complete sample of children with and without 22q11.2DS: (1) low anxiety with low depression; (2) high anxiety but low depression; (3) high depression but low anxiety; and, (4) a comorbid group of high anxiety and high depression. We further hypothesized that the majority of children with 22q11.2DS would have high anxiety and low depression and that the majority of TD children would have low anxiety and low depression.

2. Methods

2.1. Participants

The reported sample is part of a larger study on-going at the University of California Davis. Participants were 76 children with

Table 1
Means, standard deviations, and n for child self-report cluster solutions.

Group	NP[b]	Comorbid[c]	PrimAnx[d]	PrimDepr[e]
Whole group				
Anxiety[a]				
M (SD)	42.74 *(6.67)*	69.13 *(7.07)*	58.29 *(6.08)*	44.89 *(5.80)*
Depression[a]				
M (SD)	46.90 *(4.24)*	73.60 *(8.60)*	53.10 *(5.67)*	68.94 *(5.43)*
N	31	15	49	18
22q11.2DS (%)	11 *(36%)*	12 *(80%)*	35 *(71.4%)*	10 *(55.6%)*
22q11.2DS group				
Anxiety[a]				
M (SD)	35.00 *(5.18)*	68.11 *(10.86)*	62.08 *(5.38)*	–
Depression[a]				
M (SD)	41.08 *(10.52)*	79.11 *(5.28)*	54.50 *(6.70)*	–
N	25	9	34	–

[a] Anxiety, MASC total *T*-score; depression, CDI total *T*-score.
[b] NP, no pathology.
[c] Comorbid, high depression – moderate anxiety.
[d] PrimAnx, primary anxiety.
[e] PrimDepr, primary depression.

22q11.2DS (43 males; 33 females; age in yrs: $M = 11.15$, $SD = 3.40$), as confirmed by fluorescence in situ hybridization, and 55 TD children (27 males; 28 females; age in yrs: $M = 10.84$, $SD = 3.86$). Groups did not differ based on gender composition $\chi^2(1) = 0.618$, $p = 0.432$ or age $t(128) = -0.713$, $p = 0.477$. The study and all methods performed were approved by the Institutional Review Boards at the University of California, Davis and the University of New Orleans.

2.2. Psychological measures

Anxiety was assessed using self- and parent-report versions of the Multidimensional Anxiety Scale for Children (MASC) [29]. The MASC is a 39-item self-report measure consisting of four subscale domains of anxiety: physical symptoms, harm avoidance, social anxiety, and separation anxiety. Items are scored on a four-point scale ranging from 0 to 3.

The self- and parent-report versions of the Children's Depression Inventory (CDI) [30] was used to assess depression. The CDI has five subscale measures: negative mood, interpersonal problems, ineffectiveness, anhedonia, and negative self-esteem. Functional utility of the cluster groupings were determined by comparing group scores on subscales of the Behavioral Assessment Scales for Children (2nd ed.) (BASC-2) [31]. The BASC-2 consists of various subscales designed to evaluate a child's emotional and behavioral functioning.

2.3. Statistical procedures

A combination of *k* means cluster analysis and two-step cluster analysis were used to determine theoretical profiles of anxiety and depression levels in both the whole group (which consist of both TD children and children with 22q11.2DS) and within the 22q11.2DS group. The *k* means cluster analyses uses an algorithm to identify groupings of cases on various measures, which then assigns these cases to clusters based on Euclidian distances from the group center. The pseudo-*F* statistic describes the ratio of between cluster variance to within cluster variance [32], with larger pseudo-*F* values being desired, as they represent tight and distinct clusters from the different solutions. This analysis requires one to predict the number of clusters in advance, and to input that value for analysis, with the *k* representing the predicted number of clusters for the solution. To satisfy this procedure, we hypothesized that there would be four clusters for the whole group sample and four clusters for the 22q11.2 DS group. Even though both the MASC and CDI report *T*-scores based on normative data, the measures provide different ranges of scores. Therefore, the *T*-scores were standardized before analyses so that both measures had a mean of zero and a standard deviation of one. This was done to aid interpretation of symptom levels across the measures of anxiety and depression. To further validate and confirm pre-determined *k* means cluster solutions, automatic two-step cluster analyses were performed in SPSS 22 (SPSS IBM, New York, USA). This process utilizes Bayesian information criterion (BIC) to determine the number of components appropriate for a given model, in addition to delineating which solutions best matches the data for that model [33]. However, the BIC awards parsimony in the model and so will tend to favor smaller cluster numbers and so we balanced interpretation of the BIC with consistency with theoretical predictions about the cluster patterns. Following Cannon and Weems [34], we elected to use unit standard deviations of the described standardized scores for the clusters as low when the mean was below 0, moderate for between 0 and 0.70, and high when levels were above 0.70. Also, in order to identify a unique distinction of primarily anxiety or depression, a criterion for a one standard deviation difference was established, so that when one construct was above 0.70 and the other had to be below the mean. In order to identify a group as comorbid in presentation, the cluster had to present means for both anxiety and depression at or above 0.70. The same statistical parameters were applied to the parent-reported scores of the MASC and CDI for interpretation of mean scores.

3. Results

For the first hypothesis we performed cluster analysis using a predicted *k* solution of four subgroups using standardized means for CDI total depression and MASC total anxiety. We analyzed child self-report and maternal-report data separately.

3.1. Children's self-report results

For *k* means cluster, we hypothesized a four cluster solution for analysis and comparison. The empirical solution consisted of: (1) a group of children with higher anxiety/lower depression; (2) a group with primary depression (lower anxiety/higher depression); (3) a comorbid group with higher anxiety/higher depression; and, (4) a lowest anxiety/lowest depression group. A three cluster solution was explored, which revealed: (1) a group of moderate anxiety/lower depression; (2) a comorbid group of higher

depression/moderate anxiety; and, (3) a group with minimal anxiety or depression. This grouping produced lower pseudo-*F* scores than the four cluster solution and did not fit with our hypothesis. A five-cluster analysis produced a high anxiety/moderate depression group in addition to the same groups observed in the four group cluster. There was an increase in pseudo-*F* values for MASC total *T*-scores, while pseudo-*F* values for CDI total *T*-scores decreased. BIC values from the two-step analysis were used to determine the best model, with three clusters reporting the lowest value at 134.41 and four clusters reporting 137.28. Though according to the BIC the lowest number should be chosen, the difference between three and four groups is minimal compared to the other cluster groupings. Given the consistency with theory the four group [34] was retained for identifying clusters in the whole group sample. Through cross tabulation, it was confirmed that the moderate anxiety/low depression group was mostly comprised of the 22q11.2DS sample (71.4%; $n = 35$), while the low depression/low anxiety group was mostly comprised of those in the TD sample (64%; $n = 20$). The comorbid group (high depression/high anxiety) was mostly comprised of the 22q11.2DS sample (80%; $n = 12$), while the primary depression (low anxiety/high depression) demonstrated almost equal group association (22q11.2DS = 55.6%; $n = 10$).

Next, we tested the clustering solution within the 22q11.2DS group. The four cluster groups for the 22q11.2DS sample produced the same solutions as the whole sample clustering: (1) a group of children with moderate anxiety/lower depression; (2) a group with higher anxiety/lower depression; (3) a comorbid group with higher anxiety/higher depression; and, (4) a lowest anxiety/lowest depression group. A three cluster solution was investigated and this presented similar groupings as the three cluster solution applied to the whole sample of children with and without 22q11.2DS. These clusters were: (1) higher anxiety/low or no depression, (2) comorbidity (higher depression/higher anxiety), and (3) no anxiety and no depression, with the only exception being that the 22q11.2DS comorbid group presented higher *k*-means for anxiety. For the three-cluster solution, pseudo-*F* values decreased for anxiety but increased for depression. The two-cluster solution produced different pseudo-*F* values with CDI total *T*-scores increasing but MASC total *T*-scores decreasing relative to the three-group cluster.

BIC values were utilized to assess which model was most efficacious. The three group solution produced the smallest BIC value of 97.73, with minimal value changes between the two and four cluster solutions. Adolescents with 22q11.2DS report increased anxiety compared to a TD adolescent sample particularly related to academic performance and interaction with same-aged peers [35]. Other findings indicate that anxiety commonly precedes the development of anxiety in adolescents, with primary anxiety or a comorbid profile of anxiety and depression being common [30,36]. Considering this literature, we selected the three-group cluster solution (i.e. low anxiety and depression; higher anxiety and lower depression; higher anxiety and higher depression) as the most appropriate. Table 1 presents mean scores, standard deviations, and sample sizes for the whole group and 22q11.2DS samples. Cluster solutions were explored for the TD sample; however no distinct cluster groupings were produced. Figs. 1a and 2a show distribution of scores between the 22q11.2DS cluster solution and the typically developing sample on the CDI and MASC total *T*-scores.

3.2. Maternal report results

We then examined maternal reports of child anxiety and depression to determine if the same cluster groupings would be evident in the whole group (i.e. 22q11.2DS and TD) and also within each group.

For the whole group, the four cluster maternal-report solution produced similar groupings as the children's self-report groupings: (1) lower depression/lower anxiety; (2) comorbidity (higher depression/higher anxiety); (3) primarily anxiety (lower depression/higher anxiety); and; (4) moderate depression/lower anxiety. Other clustering solutions were explored using a three or five cluster solution. This also revealed similar groupings as the complete sample (i.e. 22q11.2DS and TDs combined): (1) lower depression/lower anxiety, (2) comorbid (higher depression/higher anxiety), and (3) lower depression/higher anxiety, but losing the primary depression grouping. The three cluster grouping also produced lower pseudo-*F* scores for depression but increased pseudo-*F* scores for anxiety compared to the four cluster solution. A five cluster analysis produced a moderate anxiety/low depression group in addition to the same groups observed in the four group cluster. There was an increase in pseudo-*F* values for MASC total anxiety *T*-scores, while pseudo-*F* values for CDI total depression *T*-scores decreased relative to the four group solution. BIC values reported the three cluster solution at 114.90, while the four cluster solution was reported at 120.43. Though according to the BIC the lowest number should be chosen, the difference between three and four groups was minimal compared to the other cluster groupings. Therefore, we selected the four group solution for the maternal-report data as it produced similar groupings and appropriate pseudo-*F* values compared to the self-report measures.

For the mothers of the 22q11.2DS sample, a similar four group cluster to the child-report sample was observed: (1) lowest depression/lowest anxiety; (2) primarily depression (higher depression/moderate anxiety); (3) lower depression moderate anxiety; and, (4) comorbid (highest anxiety/highest depression). A three cluster solution was also tested, which partially replicated the grouping from the self-report data with the following groups: (1) lowest depression/lowest anxiety; (2) primarily depression (higher depression/low anxiety); and, (3) primarily anxiety (high anxiety/low depression). In this clustering solution, the comorbid presentation of higher anxiety with higher depression was not found. The three group cluster solutions resulted in pseudo-*F* values of the CDI total depression increasing and MASC total anxiety decreasing relative to the four group solution. Analysis of the BIC reported the three cluster solution having the smallest value at 91.43, with minimal changes between the two and four group clusters. Table 2 presents mean scores, standard deviation, and sample size for the selected whole group and 22q11.2DS group of maternal reports. Figs. 1b and 2b show distribution of scores between the maternal report 22q11.2DS cluster solution and the maternal report typically developing sample on the CDI and MASC total *T*-scores.

Through cross tabulation, it was confirmed that based on mothers' perceptions of their child's anxiety and depression levels, children with 22q11.2DS comprised 67% ($n = 22$) of the primarily anxiety group, 64% ($n = 16$) moderate depression/low anxiety, 89% ($n = 16$) for the comorbid, and 33% ($n = 10$) fell into the no anxiety/no depression group. The majority of the no anxiety/no depression subgroup was again within the TD group (49.8%; $n = 20$).

3.3. Behavioral and IQ measures by cluster

We next conducted univariate analyses of variance (ANOVA) to determine differences of the 22q11.2DS cluster groupings, thereby validating each groups ability to predict scores on these subscales of behavior, in addition to including effect sizes. Separate ANOVAs were conducted on BASC-2 subscale scores. Significant group differences were observed for the following: Hyperactivity, $F(2,55) = 3.51$, $p < 0.05$, partial $\eta^2 = 0.11$; daily life activities, $F(2,52) = 4.58$, $p < 0.05$, partial $\eta^2 = 0.15$; functional communication, $F(2,50) = 3.76$, $p < 0.05$, partial $\eta^2 = 0.13$; and externalizing problems, $F(2,54) = 3.37$, $p < 0.05$, partial $\eta^2 = 0.11$. Post hoc analysis

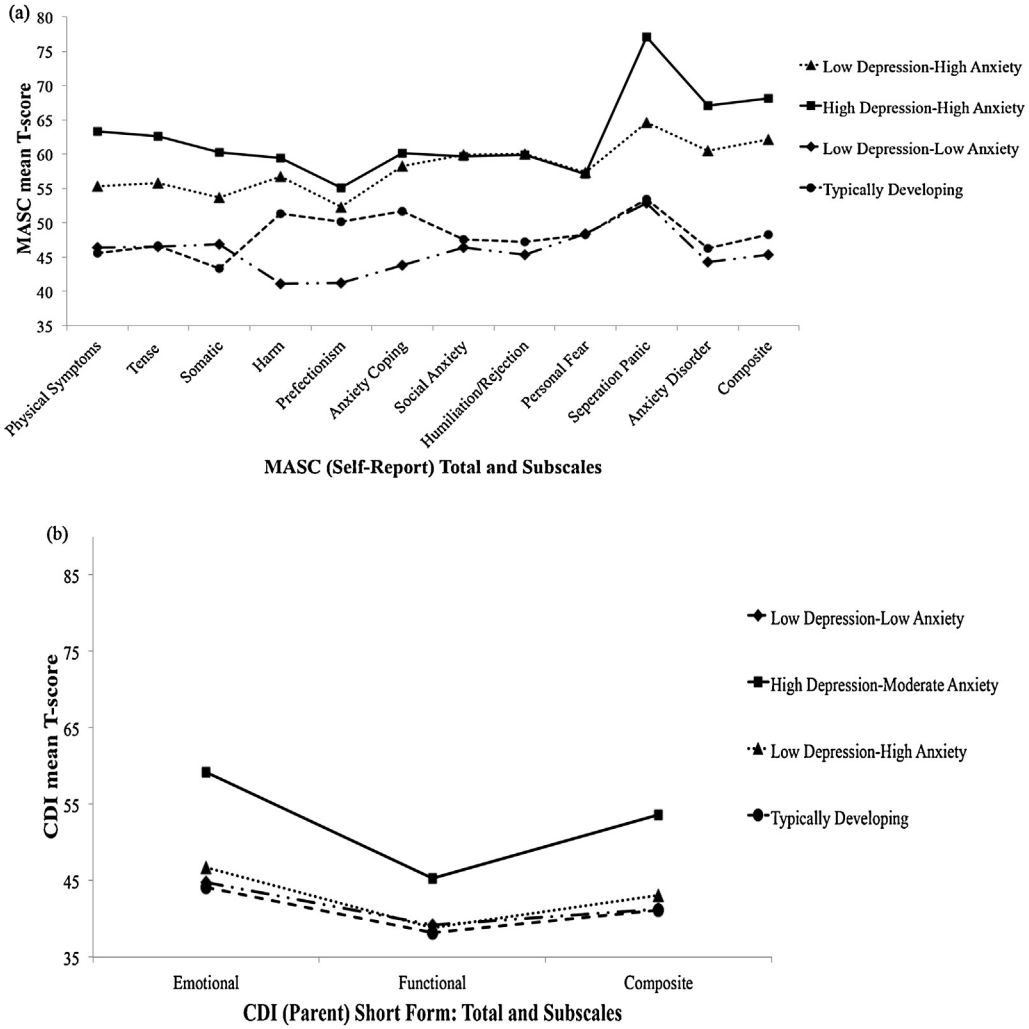

Fig. 1. Scoring distributions for 22q11.2DS child self- and mother-report group cluster solutions for total depression scores measured by the CDI. (a) 22q11.2DS self-report scoring distribution on the CDI: total and sub-scores. (b) Mothers' reports about their children with 22q11.2DS using the CDI parent form (short): total and sub-scores.

Table 2
Means, standard deviations, and n for mother-report cluster solutions.

Mother group	NP[b]	Comorbid[c]	PrimAnx[d]	PrimDepr[e]
Whole group				
Anxiety[a]				
M (SD)	44.23 *(4.75)*	64.44 *(5.83)*	63.13 *(6.86)*	47.84 *(6.53)*
Depression[a]				
M (SD)	37.70 *(3.40)*	46.83 *(4.48)*	38.77 *(3.54)*	41.60 *(5.18)*
N	30	18	30	25
22q11.2DS (%)	10 *(33%)*	16 *(89%)*	22 *(67%)*	16 *(64%)*
22q11.2DS group				
Anxiety[a]				
M (SD)	48.53 *(5.31)*	–	68.64 *(5.63)*	58.59 *(7.00)*
Depression[a]				
M (SD)	41.32 *(4.28)*	–	43.14 *(4.34)*	53.62 *(4.21)*
N	19	–	14	29

[a] Anxiety, MASC total *T*-score; depression, CDI total *T*-score.
[b] NP, no pathology.
[c] Comorbid, high depression – moderate anxiety.
[d] PrimAnx, primary anxiety.
[e] PrimDepr, primary depression.

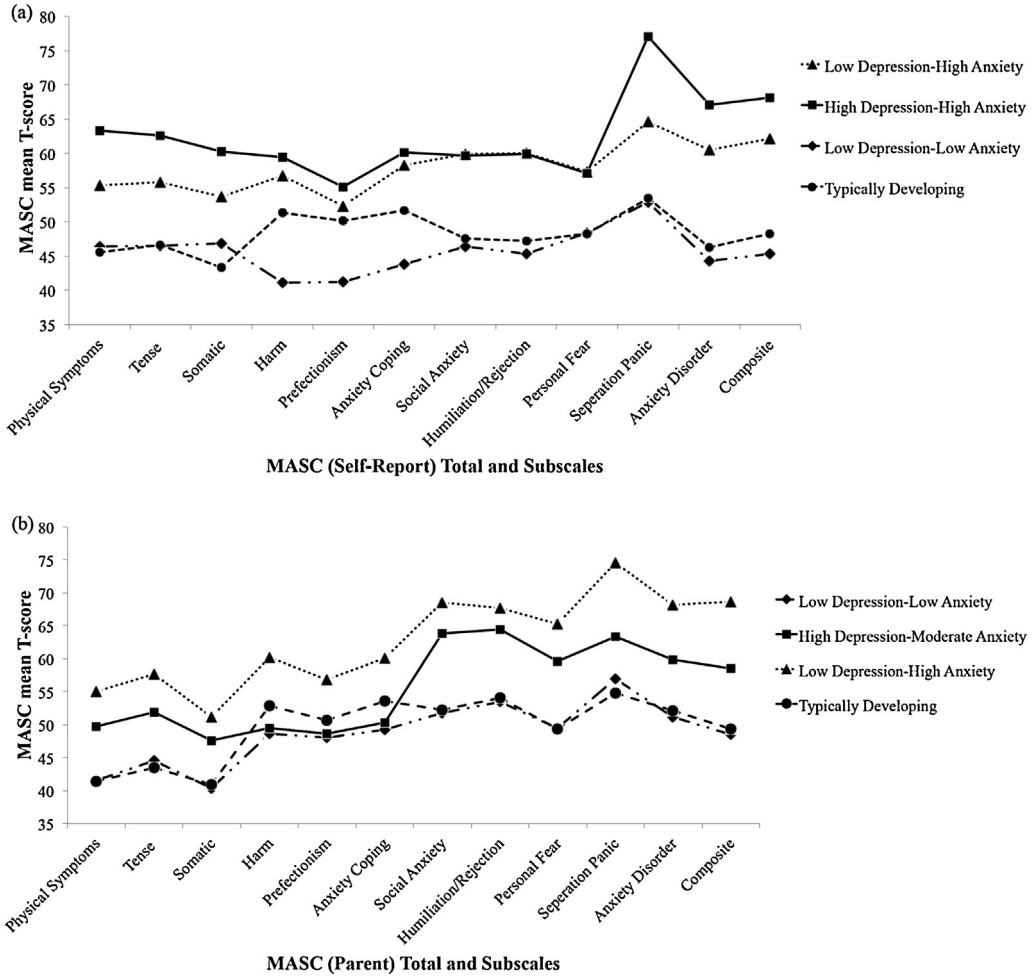

Fig. 2. Group scoring distribution for 22q11.2DS child self- and mother-report group cluster solutions for total anxiety scores measured by the MASC. (a) 22q11.2DS self-report group scoring distributions on the MASC: total and sub-scores. (b) Mothers' reports about their children with 22q11.2DS using the MASC parent-form: total and sub-scores.

Table 3
Single degree of freedom contrasts for the 22q11.2DS cluster-defined group (three-cluster analysis).

	Test variable	Mean diff.	Standard error	*p*
Comorbid/anxiety	Hyperactivity	13.18	2.41	.016*
	Functional communication	−10.47	2.08	.008**
	Externalizing problems	8.27	1.71	.037*
	Daily life activities	−13.52	1.82	.004**
Comorbid/no pathology	Hyperactivity	13.63	3.14	.016*
	Functional communication	−7.85	2.02	.052
	Externalizing problems	10.32	2.20	.013*
	Daily life activities	−9.73	2.87	.038*

Anxiety, cluster identified as primarily anxiety; normal, cluster identified as no pathology/low symptoms; comorbid, cluster identified as comorbid anxiety and depression (*$p < 0.05$; **$p < 0.01$).

using Fisher's least significant differences (LSD) revealed significant mean differences between the comorbid group and the low anxiety/depression and moderate anxiety/low depression groups, with the comorbid group demonstrating the greatest scores. Table 3 presents mean difference scores and *p* values for each of the significant contrasts. Concerning the significant findings for externalizing problems, an analysis of covariance (ANCOVA) was performed to determine if the elevated externalizing behaviors were confounded by elevated hyperactivity in the comorbid group of children. Results of the ANCOVA were not significant ($p = 0.53$) suggesting that hyperactivity was driving this association. Finally, multivariate analysis of variance (MANOVA) revealed no statistically significant differences across cluster groups on measures of full-scale ($p = 0.40$), verbal ($p = 0.78$), and performance intelligence ($p = 0.35$) or processing speed ($p = 0.22$). Finally, a linear regression was conducted to see if age predicted composite depression on the CDI. Results did not indicate a significant affect ($p = 0.74$), even when a median split on age was performed accounting for a potential binomial change in scores due to age ($p = 0.93$).

4. Discussion

To the best of our knowledge, this is the first example of using data-driven cluster analyses to reveal comorbidity subgroupings

of anxious and depressive symptoms in children with 22q11.2DS. Cluster solutions differed based on child self-report data and maternal-report data. We hypothesized that there might be a subgroup of children with elevated depressive symptoms but not elevated anxiety. This was not supported by child self-report data but was supported by maternal-report data. Based upon child self-reports of anxiety and depression, cluster analyses revealed that children with 22q11.2DS in the present sample can be divided into three subgroups: one without anxiety or depression ($n = 25$; 37% of sample), one with elevated anxiety but little or no depression ($n = 34$; 50% of sample), and one with comorbidity of elevated anxiety and elevated depression ($n = 9$; 13% of sample). Replicating previous reports of elevated anxiety in children with 22q11.2DS [37,38], the most common affective profile was that of elevated anxiety. As observed by Leyfer and Gallo [23], comorbidity of anxiety and depression might be a function of age, with pediatric populations presenting primarily anxiety, and older populations presenting comorbidity of anxiety and depression. However, this is not to say conclusively that these children do not have any depressive symptomology, as these constructs can often overlap [39], and depression usually does not present as a primary issue until adolescence [23,40]. This profile implies that currently, most of the children with 22q11.2DS in this sample present primarily higher anxiety levels compared to depression. While elevated anxiety is the predominant profile, it may precede depression in the development of comorbid symptomology [41,42]. While age was not predictive of elevated depression, the sample is relatively small and cross sectional in terms of age. Longitudinal follow-up of a larger sample of children with primarily elevated anxiety is warranted to fully test this hypothesis.

Mothers' perceptions of their children's anxiety and depression did not reveal a comorbid higher anxiety and higher depression cluster as predicted. Along with inherent limitations of using self-report measures in general, previous studies have demonstrated a disparity between self-report and parent-reported assessments of child behavioral pathology [43,44]. Briegel and colleagues [36,45] found that parents of children with 22q11.2DS are more likely to rate their child's internalizing behaviors as a concern. In contrast to the 22q11.2DS group, the clustering solutions for mothers of typically developing children produced two cluster groupings, with a subset of mothers overestimating their child's level of depression (33.3%; $n = 15$). This could potentially highlight a differentiation in attending to and awareness of a child's issues as parents of children with developmental and chronic medical issues appear to be more perceptive and aware of the emotional states of their children [46–48]. This attentiveness likely arises as a component of the considerable parental investment needed for parents of children with developmental issues [49]. Further investigation should include paternal- or sibling-report of affect and behavior of children with 22q11.2DS, examining what is likely a complex interpersonal dynamic between parents and siblings of children coping with a developmental disorder [50,51]. Furthermore, that some children had neither anxiety nor depression highlights the variable nature of 22q11.2DS with some children doing quite well emotionally. Further study of the children with low or no anxiety or depression may provide insights into protective factors and interventions for children experiencing more difficulties.

Similar to previous findings [1,13], children with higher anxiety and depression also scored higher on scales of hyperactivity and externalizing problems, had poorer functional communication, and reduced ratings of daily life activities. Symptoms of anxiety and depression are characteristic of internalizing behavior [52]. Yet, the higher anxiety and depression group was rated as having more externalizing problems. Comorbidity of internalizing such as anxiety, depression, and withdrawal and externalizing behaviors such as aggression with attention difficulties has been reported [53]. Also, anxiety and sadness could arise from loneliness and social rejection associated with peer rejection as a result of elevated externalizing behavior in a feed-forward manner [54]. This coincides with literature describing the magnified effect that anxiety and depression can have on behavioral [55,56] and communication impairments [57]. These difficulties likely exacerbate anxiety and depression as the negative consequences of behaviors are reflected back to a child with diminished coping and communication capacity. Furthermore, children with 22q11.DS have been assessed to have temperaments that are somewhat difficult. In a study of TD children ages four to eight by Eisenberg and colleagues [58], mothers and teachers who rated children as high on anger and low on self-regulation were more likely to rate those children as externalizing rather than internalizing. Antshel and colleagues [59] found that parents rated their children with 22q11.2DS as having poorer sustained attention, irregular daily habits, as less cheerful and pleasant, and inflexible to change. Thus, mothers in the current study may be responding to questions on the BASC-2 in a way that highlights traits that may manifest as externalizing such as tantrums or anger in their children. Finally, it is important to point out that while subgroups of children differed in terms of anxiety and depression in statistically measurable ways, as a group, composite anxiety and depression levels were below clinical concern with significant variability across individuals. While anxiety and depression may have been higher in a given subgroup, it may not result as a group in elevated internalizing behaviors as measured by the BASC-2.

Comorbidity of anxiety and depression in childhood and adolescence could, over time, contribute to a developmental trajectory leading to a schizophrenia spectrum disorder as evidenced in adults who have comorbid anxiety and depression [1]. Clearly, not all children with 22q11.2DS and an anxiety disorder go on to develop psychosis in adulthood. Thus, an important next step is determining the mechanisms by which anxiety and depression increase risk for psychopathology. Anxiety and depression are affective states that are both indicative of and contribute to stress. A stressful life history of early and serious medical intervention, and impairments in cognitive and socioemotional development may contribute to risk of psychosis in this population [27]. Anxiety and depression may arise from limited stress coping resources in the face of what could be considered 'inescapable' stressors associated with increasing complexity of the social and educational environment for the child with 22q11.2DS. Interestingly, intelligence measures did not differ across subgroups regardless of anxious and depressive symptom comorbidity. This suggests that behavioral impairments are not simply a result of global cognitive impairment in these children. This corroborates findings by Angkustsiri and colleagues [14] that anxiety rather than intelligence, was a better predictor of behavioral and functional impairments in children with 22q11.2DS.

The present study highlights the opportunities for utilizing data from a variety of domains to gain a more nuanced understanding of the etiopathology of schizophrenia in a high-risk population. The syndrome associated with the 22q11.2 chromosomal deletion is in itself complex and heterogeneous. The majority of children with 22q11.2DS do not develop adult psychosis and there are many with schizophrenia without the deletion. Nevertheless, children with 22q11.2DS provide an optimal model for the study of the etiopathology of schizophrenia as their development can be followed long before clear manifestations of the disease. The difficulty lies in determining which children are at greatest risk in adulthood. Reducing some of this heterogeneity can be achieved by statistical methods such as cluster analysis to find groups of children at increased vulnerability in an already vulnerable population. A role for stress as a contributing risk factor for schizophrenia has been suggested for children with 22q11.2DS [27]. Depression and anxiety can arise from stress and likely further contribute to stress

as these emotional states manifest in the development abnormal behavior.

The present study is not without limitations. Structured diagnostic interviews were not conducted and the use of self- and parent-report measures may have issues with validity especially in a population of children with below-average intelligence. Composite anxiety and depression scores were used to generate cluster patterns that do not provide nuanced insight into the type of anxiety or depressive symptoms children and their mothers are reporting. Finally, though a similar clustering of anxiety and depression levels were found between self-report and parent-reported scores of those with 22q11.2DS, additional factors could be contributing. Specifically, externalizing and internalizing behaviors often displayed in children with 22q11.2DS can increase stress in the parents, possibly influencing their assessment of the presence and severity of behavioral issues. Future research should investigate how child reported indices of anxiety and depression corroborates with parental self-reported levels of anxiety and depression, possibly demonstrating a cyclical relationship of increased behavioral issues in children influencing parental mood, which may further exacerbate the child's behavior [60].

Effective interventions for anxiety and depression exist and early intervention could reduce the risk of developing psychopathology in adulthood while improving current quality of life. Future work should focus on examining the interplay between anxiety, mood, and specific behaviors to determine the reciprocity of these domains in children with 22q11.2DS. For example, improving functional communication skills will likely improve social and behavioral difficulties and coping [57,61] thus improving quality of life in the short-term and potentially reducing risk of adult psychopathology.

Authors' contributions

DDS performed the statistical analyses, data interpretation, and wrote the first draft of the manuscript. EAB, CFW, and DDS conceived of and designed the study. EAB and TJS acquired the funding. EAB, TJS, and KA generated the experimental task. DDS, TJS, EAB, CFW, and KA supported data interpretation and manuscript revision. TJS, EAB, and KA recruited all children and oversaw analyses and testing. All authors read and approved the final manuscript.

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