4-2010

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Published in final edited form as:
J Am Acad Child Adolesc Psychiatry. 2010 April ; 49(4): 333–344.

Cognitive and Psychiatric Predictors to Psychosis in Velocardiofacial Syndrome: A 3-year follow-up study

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Abstract

Objective—To predict prodromal psychosis in adolescents with velocardiofacial syndrome (VCFS).

Method—70 youth with VCFS, 27 siblings of youth with VCFS and 25 community controls were followed from childhood (Mean age = 11.8 years) into mid-adolescence (mean age 15.0 years). Psychological tests measuring intelligence, academic achievement, learning/memory, attention and executive functioning as well as measures of parent and clinician ratings of child psychiatric functioning were completed at both time points.

Results—Major depressive disorder, oppositional defiant disorder and generalized anxiety disorder diagnoses increased in the VCFS sample. With very low false positives, the best predictor of adolescent prodromal psychotic symptoms was parent ratings of childhood odd/eccentric symptoms and child performance on a measure of executive functioning, the Wisconsin Card Sorting Test.

Conclusions—Similar to the non-VCFS prodromal psychosis literature, a combination of cognitive and psychiatric variables appears to predict psychosis in adolescence. A child with VCFS who screens positive is noteworthy and demands clinical attention.

Keywords

Velocardiofacial syndrome (VCFS); 22q11 deletion syndrome; cognition; psychosis; longitudinal

Velo-cardio-facial syndrome (VCFS) is caused by an interstitial deletion from chromosome 22 at the 22q11 band. The most common microdeletion syndrome yet identified in humans, VCFS has a population prevalence of approximately 1:2000 to 1:6000 live births [1, 2]. In most cases, VCFS is caused by a hemizygous deletion of 3 million base pairs of DNA encompassing 40 genes but approximately 8% have smaller nested deletions of 1.5 million base pairs spanning 34 genes [3]. Structural anomalies affect nearly every part and system of the body and may

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Disclosure: Dr. Faraone, in the past year, has received consulting fees and has been on Advisory Boards for Eli Lilly, Ortho-McNeil, and Shire Development, and has received research support from Eli Lilly, Pfizer, Shire and the National Institutes of Health. In previous years, Dr. Faraone has received consulting fees or has been on advisory boards, or has been a speaker for the following sources: Shire, McNeil, Janssen, Novartis, Pfizer, and Eli Lilly. In previous years he has received research support from Eli Lilly, Shire, Pfizer and the National Institutes of Health. Drs. Antshel, Shprintzen, Fremont, and Kates, and Ms. Higgins report no biomedical financial interests or potential conflicts of interest.

include congenital heart disease, palatal defects, thymic hypoplasia, and endocrine disorders [1]. VCFS is the most common genetic cause of conotruncal heart anomalies and the most common genetic cause of cleft palate [4].

VCFS is associated with a distinctive cognitive phenotype. Full scale IQ's are commonly in the Borderline range of functioning (IQ 70–75) [5–11]. Reading, spelling and phonological processing skills as well as rote auditory/verbal memory are relatively spared in VCFS [5, 11–17]. Conversely, math learning disabilities [5, 11, 12, 17–22], visuospatial deficits [14, 17, 18], attention deficits [11, 19, 23, 24] and executive function deficits in domains such as cognitive flexibility, response inhibition and nonverbal working memory have been reported to be an area of weakness in the VCFS cognitive profile [11–13, 15–17, 19, 25–28].

The most commonly reported psychiatric disorders are attention deficit/hyperactivity disorder (ADHD) (present in 30–40% of individuals with VCFS) [29–31], anxiety disorders, especially simple phobias and separation anxiety (present in 30–40%) [10, 30, 32, 33], autism spectrum disorders (10–30%) [34, 35], mood disorders including major depression and bipolar disorder (present in 20–30%) [30, 36] and psychotic disorders (25–30%) [37, 38].

Clearly, the most worrisome feature of the VCFS behavioral profile is the elevated risk for schizophrenia and psychosis. The age of onset varies between early adolescence and early adulthood, with most onsets occurring in the late teens and early 20's [39–41]. More mild, subthreshold psychotic symptoms occur in 30–50% of youth with VCFS [10, 42]. Unlike many psychiatric disorders (e.g., ADHD, anxiety, depression, etc.), the increased risk for schizophrenia appears more specific to VCFS rather than a function of developmental delays. In other words, individuals without VCFS who have mental retardation/developmental delays have more symptoms of psychopathology such as inattention, hyperactivity, anxiety, etc. than average IQ individuals [43]; psychotic symptoms, however, are not generally elevated in the non-VCFS mental retardation/developmental disorder population [43].

The catechol-O-methyltransferase (COMT) gene is located on chromosome 22q11. The COMT gene is located in the 1.5 Mb VCFS microdeletion region. Thus all individuals with this disorder have only one copy of this gene, suggesting that COMT may be a candidate gene for psychosis in VCFS. The Val-108/158-Met COMT polymorphism has received empirical attention as a possible risk factor for psychosis. This polymorphism has been associated robustly with prefrontal cognitive functions in typical children [44] and adults [45]. Homozygosity for the Met allele is associated with optimal cognitive function, evidence for its association with psychosis is more variable [46]. However, findings from studies of the effect of COMT polymorphisms on cognition and psychosis in VCFS have not been consistent. Whereas a study by Gothelf and colleagues [47] suggested that individuals with VCFS who have the low-activity (Met) allele of the COMT gene had a more significant decline in Verbal IQ scores and had more severe psychotic symptoms than those carrying the high-activity (Val) allele, other studies have found either the opposite [48] or no [49, 50] effect of COMT on cognition and psychosis.

Only one longitudinal study of youth with VCFS has been published. Those findings suggested that at Time 1 (late childhood), subthreshold psychotic symptoms, anxiety (especially OCD) and depression symptoms, and lower verbal IQ scores predicted the onset of psychotic disorders in adolescence [47]. The purpose of the present investigation was to attempt to replicate these data using a larger sample with more neuropsychological and psychiatric dependent variables. Given the greatly elevated risk for psychosis, the substantial percentage of children and adolescents with VCFS who have ADHD, major depressive disorder, anxiety disorders and oppositional defiant disorders and the relative frequency of VCFS, a study of VCFS seems an important topic for child and adolescent psychiatrists. Moreover, given both the importance of

early intervention in psychosis [51] and the critical shortage of child and adolescent psychiatrists [52], efforts to predict psychosis in the VCFS population seem clinically-relevant.

Method

Participants

Participants were enrolled in the longitudinal study of risk factors for psychosis in VCFS. At time 1, 80 youth with VCFS (Mean age = 11.9 years, SD = 2.2), 33 siblings of youth with VCFS (sibling control; Mean age = 12.2 years, SD = 1.9) and an age, gender and socioeconomic status matched group of 40 non-VCFS youth (community control; Mean age = 12.0 years, SD = 1.9) participated. No age differences existed between the groups at Time 1, F (2, 158) = 0.24, p = .784, η^2 = .01.

At Time 2, 70 youth with VCFS (Mean age = 15.0 years, SD = 2.1), 27 siblings of youth with VCFS (Mean age = 15.0 years, SD = 1.9) and 25 community controls (Mean age = 14.7 years, SD = 1.4) were included in the analyses. No age, F (2, 120) = 0.44, p = .647, η^2 = .01, or gender differences, χ^2 (df = 2) = 0.9, p = .641, existed between the groups at Time 2. Please see Table 1 for complete participant information.

An independent samples t-test indicated that there were no differences in attrition between our three groups, t (2) = 3.06, p = .263. Furthermore, participants lost to follow-up did not differ from those who did follow-up on any relevant Time 1 sociodemographic measures including participant age, gender, and socioeconomic status. In addition, participants lost to follow-up did not differ from those who did follow-up on any relevant Time 1 psychiatric or cognitive variables. Thus, those participants who completed Time 2 assessments appear representative of the broader Time 1 sample.

Procedures

Participants were assessed at two time points, with approximately three years between time points. At Time 2, all involved research personnel were blinded to Time 1 findings. Informed consent/assent was obtained from parents and children under protocols approved by the institutional review board.

Each child enrolled in the study was administered a neuropsychological test battery that included tests of cognitive function, academic achievement, executive function, sustained attention, working memory and learning. Psychological testing was followed by a structured psychiatric interview, administered by a clinical psychologist or a board-certified child psychiatrist. After completing the psychological and psychiatric assessments, the participating children had a magnetic resonance imaging (MRI) scan of his or her brain. Finally, all VCFS participants had a blood draw. This blood sample and resulting DNA sample was processed to genotype the COMT Val-108/158-Met COMT polymorphism. Our genotyping methods have been previously described in full detail elsewhere [53].

Cognitive and Psychiatric Assessment Tools

Unless otherwise noted, all instruments were administered at both Time 1 and 2.

Cognitive—Measures of general intellectual functioning were the Wechsler Intelligence Scale for Children —Third edition (WISC-III) [54] or Wechsler Adult Intelligence Scale – Third edition (WAIS-III) [55]. The WISC-III was administered to all participants at Time 1, and to participants at or under the age of 16 years, 11 months at Time 2. The WAIS-III was administered to all participants over the age of 16–11 at Time 2. Comparative studies between the Wechsler child and adult intelligence scales suggest that relative to WISC-III scores, WAIS-

III scores are inflated between three and seven points [56–58]. Accordingly, for our data analyses, we subtracted five points from WAIS-III full-scale, verbal and performance IQ scores.

Academic achievement was assessed using the Wechsler Individual Achievement Test-Second edition(WIAT-II) [59]. Attention was assessed using the Gordon Diagnostic System - Continuous Performance Test (CPT) [60]. Executive functioning was assessed with the Wisconsin Card Sorting Test (WCST) [61] and Tower of London (TOL).

Learning and memory was assessed with the California Verbal Learning Test (CVLT) [62] and the Visual Span Test [63]. (The Visual Span is a computer-presented adaptation of the Visual Memory Span subtest of the Wechsler Memory Scale-Third Edition, produced on the Colorado Assessment Tests. An irregular array of squares is displayed on the screen, a subset of them is illuminated briefly, and the subject must reproduce these sequences of increasing length. Forward and backward span scores are obtained.)

Psychiatric—The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) [64] was utilized to make DSM-IV [65] psychiatric diagnoses. The child's primary caregiver (almost always his/her mother) was interviewed with the K-SADS-PL. Every attempt was made to interview the child, but in many cases the child had difficulty responding; in these cases, the K-SADS-PL data was based on the parent's response. A child and adolescent psychiatrist or clinical child psychologist administered the KSADS assessment. Inter-rater reliability, which was calculated for 10 interviews, and assessed with the Kappa coefficient, was .91.

The Scale of Prodromal Symptoms (SOPS) [66] was used to assess prodromal psychotic symptoms. The SOPS consists of four domains, in which the clinician rates (based on self-report and observation) each participant and derives summary scores for positive prodromal symptoms (e.g., grandiosity, hallucinations) negative prodromal symptoms (e.g., withdrawal, avolition), disorganization (e.g., odd behavior, bizarre thought) and general symptoms (e.g., sleep disturbance, dysphoric mood). The SOPS was administered to all participants at Time 2 by a doctoral-level clinician during the structured psychiatric interview. Inter-rater reliability, based on five SOPS interviews and assessed with the intraclass correlation coefficient, was 0.90. Since many of the children in our study had difficulty responding to a psychiatric interview, we reworded the questions in this scale to allow us to administer it to the child's parent. Ratings were based on a Likert-type scale, with scores that ranged from zero to four for each symptom. Summary scores for the four symptom domains were calculated. Our primary reason for utilizing the SOPS was to predict prodromal symptoms; thus, we only used the summary scores from the positive, negative and disorganization subscales. Our SOPS Total scores are based upon the aggregate of these three subscales. In addition, given that positive symptoms are the most specific to psychosis, several of our analyses used this subscale as an outcome measure. Using a method with a precedent in the literature [66], we identified positive prodromal symptoms as one or more of the five SOPS positive symptom items as being rated a '2' or higher.

The Premorbid Adjustment Scale (PAS) [67] evaluates the achievement of developmental goals from childhood into adulthood in persons who eventually develop schizophrenia. Although the scale was originally designed as a retrospective instrument to assess premorbid functioning up to six months prior to a psychiatric hospitalization, we used the scale prospectively, rating each participant on the items corresponding to his or her current age. The scale focuses on five areas of functioning: social accessibility-isolation; peer relationships; school functioning; ability to function outside the nuclear family; and the capacity to form intimate socio-sexual ties. Ratings were based on data obtained during the K-SADS-PL. Ratings for each item were anchored to descriptive phrases, ranging from 0 (representing "healthiest" functioning) to 6

(representing most impaired functioning). Ratings were summed and then divided by the total number of items, producing a ratio ranging from 0 (healthy functioning) to 1 (poor functioning). Inter-rater reliability, for ten participants between two doctoral level raters, calculated using an intraclass correlation coefficient of item ratings, ranged from .85 to .90.

Finally, the Behavior Assessment Scale for Children (BASC) – Parent report version [68] was administered to provide a continuous measure of adaptive and problem behaviors. Each of the 130 items of the child version of the BASC is rated on a 4-point frequency scale, ranging from *never* to *almost always*.

Data Analyses

To create a standard metric across all psychological tests, all scores were converted to z-scores. Changes in performance as a function of time were calculated by subtracting Time 1 performance (z-score) from Time 2 performance (z-score). Thus, positive values indicate stronger performance at Time 2.

McNemar non-parametric tests for related samples were computed to compare KSADS diagnostic consistency across time. Separate tests were computed for each sample. Then, to analyze between group changes across time, a logistic regression for each psychiatric diagnosis was computed using Time 2 psychiatric diagnosis as the outcome measure and Time 1 diagnosis by group interaction as the predictor.

Repeated-measures multivariate analyses of variance (MANOVA) models, with diagnostic group as the main effect, and psychological test scores or behavioral variables and time as repeated factors were computed. Group and time effects and group-by-time interaction were examined. In order to test the association between SOPS scores and behavioral/cognitive variables, we conducted Zero-inflated Poisson regression analyses [69]. The choice of the Poisson regression was based on the distribution of our SOPS data, for which at least 50% of scores equaled zero (indicating the absence of any prodromal symptoms). We initially performed the Vuong test in order to determine if the proportion of scores equaling zero warranted the traditional Poisson regression analysis or the zero-inflated Poisson regression analysis. Based on the results of the Vuong test, we conducted the zero-inflated Poisson analysis for all variables of interest (using Stata 10.0). Finally, sensitivity, specificity, negative predictive power (NPP) and positive predictive power (PPP) analyses were conducted to help determine the clinical utility of a measure to predict psychosis.

Results

Longitudinal Changes in Psychiatric Status

At Time 1, the most common psychiatric diagnoses in the VCFS sample were ADHD, major depressive disorder, phobias and generalized anxiety disorder. As demonstrated in Table 1, four Axis I conditions changed across time within the VCFS sample. Major depressive disorder ($p < .001$), oppositional defiant disorder ($p = .008$) and generalized anxiety ($p = .040$) diagnoses increased in prevalence. No youth with VCFS who had a Time 1 major depressive disorder, oppositional defiant disorder or generalized anxiety diagnosis lost their diagnosis at Time 2. Thus, the differences were due to additional youth with VCFS acquiring the diagnosis at Time 2. In the sibling group, the one participant who had a Time 1 major depressive disorder diagnosis maintained the diagnosis at Time 2; in addition, 7 sibling participants who did not have a Time 1 major depressive disorder diagnosis had a Time 2 diagnosis ($p = .032$).

No controls or siblings gained an ADHD diagnosis; although approaching significance ($p = .094$), 7 of 15 control participants who had a Time 1 ADHD diagnosis did not have a Time 2 ADHD diagnosis. Two of the 4 sibling participants who had a Time 1 ADHD diagnosis did

not have a Time 2 ADHD diagnosis ($p = .125$). In the VCFS sample, 12 of the 36 participants who had a Time 1 ADHD diagnosis did not have a Time 2 ADHD diagnosis ($p = .096$). However, unlike the sibling and control samples, five youth with VCFS had a Time 2 ADHD diagnosis yet not a Time 1 ADHD diagnosis. See Table 1 for complete KSADS data and McNemar analyses.

To assess between group changes, logistic regressions were computed using Time 2 psychiatric diagnosis as the outcome measure and Time 1 diagnosis by group interaction as the predictor. To limit our number of analyses, mood and anxiety disorders were considered collectively, yet are reported in Table 1 individually. Two psychiatric diagnostic categories had psychiatric diagnosis × group interactions; mood disorders increased in the VCFS and sibling groups relative to the control group, Wald $\chi^2 = 11.43$, $p < .001$, and anxiety disorders increased VCFS group relative to both other groups, Wald $\chi^2 = 6.03$, $p = .018$.

Longitudinal Changes in Cognition

As shown in Table 2, several Time × Study Group psychological test performance interactions emerged on measures of intelligence, on the full scale, verbal comprehension and perceptual organization indices, community controls improved more robustly than both VCFS and sibling control participants. On the academic measure, only the VCFS group improved in reading. On the Visual Span, control participants improved by one-half of a standard deviation, whereas sibling controls showed no change and VCFS participants decreased slightly. On the WCST, both VCFS and sibling participants improved on perseverative error performance while controls did less well. No interactions emerged on the CVLT, Continuous Performance Test and Tower of London. All groups did less well at Time 2 on the CVLT, although declines in scores were sharper for sibling and VCFS participants than for controls. All study groups improved from Time 1 to Time 2 on the Continuous Performance Test and Tower of London. Complete results are detailed in Table 2.

Multiple time × gender interactions occurred; across several psychological tests, female performance declined more than males. However, no time × gender × diagnosis interactions emerged.

Longitudinal Changes in Behavior

As shown in Table 3, no interactions emerged on the parent report of child behaviors on the BASC as a function of time. Additionally, no time × gender × diagnosis interactions emerged.

Predicting Time 2 Prodromal Symptoms From Time 1 Cognitive and Behavioral/Psychiatric Variables

At Time 2, no sibling controls and one community control had any positive or disorganized prodromal symptoms. Given our lack of prodromal symptoms in both control groups, analyses predicting prodromal symptoms only included VCFS participants. See Table 4 for SOPS total scores and subscales (positive, negative, disorganized) for each of the three groups (VCFS, siblings and community controls)

As shown in Table 5, several Time 1 psychological test variables predicted Time 2 prodromal symptoms. In order of predictive power, Time 1 performance on the Visual Span Backward, WISC-III Verbal Comprehension Index, WISC-III Processing Speed Index, Visual Span Forward, WCST Perseverative Errors Standard Score and Stroop Color-Word Interference T-Score all significantly predicted Time 2 prodromal symptoms. Across all psychological tests, lower performance at Time 1 predicted more Time 2 prodromal symptoms.

Behaviorally, as seen in Table 3, higher Time 1 levels of odd/eccentric and anxious behaviors were significant BASC predictors of prodromal symptoms at Time 2. Lower clinician ratings on the CGAS and PAS at Time 1 were also significant predictors of Time 2 prodromal symptoms.

Predicting Positive Prodromal Symptoms Time 1 Variables

Given the specificity of positive symptoms towards a diagnosis of a psychotic disorder, we recomputed our Poisson regression models using SOPS positive symptoms as the outcome variable and Time 1 cognitive and behavioral variables as predictors. In order of predictive power, the WCST Nonperseverative Error Standard Score ($z = -3.25$, $p < .001$), the Tower of London Total Number of Moves ($z = 2.18$, $p = .029$) and CPT number of errors of omission ($z = 2.18$, $p = .029$) were significant predictors of Time 2 positive symptoms. Across all three psychological tests, worse performance at Time 1 was predictive of higher number of SOPS positive symptoms at Time 2.

Behaviorally, the Time 1 BASC Atypicality Scale ($z = 3.55$, $p < .001$) and the PAS ($z = 3.71$, $p = .002$) were both significant predictors of Time 2 SOPS positive symptoms.

Impact of Val/Met Status on Prodromal Symptoms

In our VCFS sample, all of whom were deleted for one copy of the *COMT* gene, 39 of the participants had the Val allele on the intact chromosome 22 and 23 had the Met allele. There were no age differences between youth with the two alleles, $F(1, 66) = 0.14$, $p = .871$, $eta^2 = .00$. More males have the Val allele ($n = 17$) and more females ($n = 24$) have the Met allele, $\chi^2 = 7.63$, $p = .022$. There were no differences between SOPS prodromal symptoms and Val and Met allele status, $F(1, 66) = 0.71$, $p = .402$, $eta^2 = .01$.

Predicting Time 2 Major Depressive Disorder Diagnosis From Time 1 Variables

Given that 64% of our VCFS and 30% of our sibling participants met DSM-IV diagnostic criteria for a major depressive disorder diagnosis at Time 2, we sought to examine Time 1 variables which may be significant predictors. No Time 1 cognitive or behavioral variables predicted a Time 2 major depressive disorder diagnosis in the sibling group.

In the VCFS group, two Time 1 cognitive variables significantly predicted a Time 2 major depressive disorder diagnosis: WISC-III Processing Speed (Wald $\chi^2 = 5.45$, $p = .011$) and Visual Span Backward (Wald $\chi^2 = 4.87$, $p = .020$). Several Time 1 behavioral and psychiatric variables predicted a Time 2 major depressive disorder diagnosis (in order of predictive power): BASC Anxiety (Wald $\chi^2 = 14.02$, $p < .001$), BASC Withdrawal (Wald $\chi^2 = 12.44$, $p < .020$), BASC Social Skills (Wald $\chi^2 = 11.76$, $p < .001$), a Time 1 ADHD diagnosis (Wald $\chi^2 = 9.87$, $p < .001$) and CGAS (Wald $\chi^2 = 5.54$, $p = .023$).

Sensitivity/Specificity/PPP/NPP

Using a criterion with a precedence in the literature [66], we grouped participants with VCFS into two groups: those with significant positive prodromal symptoms ($n = 14$) and those without ($n = 56$). Using the highest predictor of the SOPS Positive symptoms in the Poisson analyses, we established a classification of BASC Time 1 Atypicality Scale $T \geq 70$ to determine the sensitivity, specificity, positive predictive power (PPP), and negative predictive power (NPP) of a Time 1 BASC Atypicality score in the 'Clinical' range towards predicting Time 2 positive prodromal symptoms. Using this classification, the Time 1 BASC Atypicality $T \geq 70$ had a sensitivity of 43% and a specificity of 90%. The PPP of the Time 1 BASC Atypicality $T \geq 70$ was .91%, indicating that if the Time 1 BASC Atypicality was greater than 70, there is 91% likelihood that prodromal symptoms emerged at Time 2. The NPP of the Time 1 BASC

Atypicality T ≥ 70 was found to be 42%, signifying a 42% chance that a participant deemed 'non-clinical' on the basis of the Time 1 BASC Atypicality will be non-prodromal at Time 2.

While these results demonstrate strong specificity and PPP of a BASC Time 1 Atypicality Scale T ≥ 70 towards predicting Time 2 prodromal symptoms, the sensitivity and NPP of this scale alone is less than ideal. Thus, to further guide clinicians, our sensitivity, specificity, PPP and NPP statistics were recalculated using both a BASC Time 1 Atypicality Scale T ≥ 70 and the highest cognitive predictor of the SOPS Positive symptoms, the WCST Nonperseverative standard score one standard deviation below the mean (≤ 85). Using this combination of both behavioral and cognitive measures, the sensitivity of predicting Time 2 prodromal symptoms improved to 79% with a specificity of 95%. The PPP of 96% and NPP of 78% were similarly improved.

Discussion

Psychiatric and Cognitive Functioning

Prodromal symptoms—While no adolescents with VCFS were diagnosed with a psychotic disorder, significant prodromal psychotic symptoms were observed in approximately 20% of our VCFS sample. This prevalence rate of prodromal psychotic symptoms is somewhat below what others have reported (30–50%) [10, 42] and may be a function of our relatively strict criterion for operationalizing prodromal symptoms.

Childhood performance on several tests of executive functioning and verbal abilities best predicted prodromal symptom levels in adolescence. Across all tests, lower performance during childhood predicted more prodromal symptoms in adolescence. This finding is entirely consistent with other VCFS research [47] as well as the non-VCFS schizophrenia research [70–83]. Thus, our data are entirely consistent with the extant non-VCFS high risk data; language and executive function deficits in childhood appear to presage which children with VCFS will develop significant prodromal psychotic symptoms in adolescence.

Behaviorally, a child with VCFS who has high levels of odd/eccentric and anxious behaviors may be at greatest risk of developing significant prodromal psychotic symptoms in adolescence. Once again, this finding is entirely consistent with other VCFS longitudinal data [47] as well as the non-VCFS schizophrenia research [84–89].

While certainly needing replication, our data suggest that mental health clinicians working with children with VCFS may wish to employ the BASC and WCST. A childhood BASC Atypicality T ≥ 70 score alone had strong specificity (90%) and PPP (91%) yet when a WCST Nonperseverative error (≤ 85) was added, the strong specificity and PPP were maintained and the sensitivity improved to 79% and the NPP (78%) also improved. Adding the WCST to the screening assessment improved the sensitivity and NPP suggesting that for maximal predictive power, clinicians may wish to use both the BASC and WCST.

Internalizing disorders—Children with VCFS, as they aged into adolescence, were more likely to be diagnosed with major depressive disorder and generalized anxiety disorder diagnoses. Our prevalence rate of major depressive disorder (64%) is somewhat higher than data recently published on a large cohort of individuals with VCFS [90]. In that study, 40% of late adolescents with VCFS were diagnosed with depression [90]. In that same study, anxiety disorders were the most common psychiatric diagnosis with prevalence rates ranging from 42–60% depending on age [90]. Our data (53%) are entirely consistent with these prevalence rates and suggest that a majority of adolescents with VCFS will have a mood and/or anxiety disorder.

Siblings of youth with VCFS were also more likely than controls to be diagnosed with major depressive disorder in adolescence. No childhood cognitive or behavioral variables predicted adolescent depression in the siblings. This is an interesting finding which requires replication. However, it may be that growing up in a house with a child with VCFS is a chronically stressful experience which can lead to depressed mood. Future research should consider how VCFS affects the entire family system.

In the VCFS sample, child performance WISC-III processing speed and performance on a nonverbal task of working memory (Visual Span Backwards) were both significant predictors of adolescent depression in the VCFS group. Behaviorally, having high levels of anxiety, social withdrawal as well as having poor social skills and an ADHD diagnosis appear to be predictive of becoming depressed in adolescence. Other non-VCFS longitudinal research has similarly suggested that childhood levels of anxiety and social withdrawal [91, 92] as well as an ADHD diagnosis [93] all confer increased risk for depression in adolescence.

Cognitive functioning—While cross-sectional data [90] including our own work [5] suggest a negative association between cognitive functioning and age, our longitudinal data suggest that not all cognitive functions may be equally affected. Wechsler Full Scale IQ, Processing Speed and Freedom from Distractibility indices all decreased significantly across age. CVLT performance and math academic attainment also significantly dropped over time. Nonetheless, performance on WCST Perseverative errors, Tower of London and reading attainment all significantly improved as a function of age. Thus, it does not appear that all cognitive functions decline as a function of age. Nonetheless, IQ scores have been traditionally used far more often as an outcome measure than any of the other test (and were the only cognitive variable included in the large cross-sectional study [90].

Also of interest is our finding that females with VCFS declined more than males with VCFS across multiple psychological tests. This may help to explain the relatively inconsistent finding in the literature; some research groups including our own have reported that males with VCFS are more cognitively affected than females with VCFS [5, 94]. Other groups, however, have failed to report such sex differences [11, 95]. It is possible that the age of the participants in the study may be a factor which helps to explain this relatively inconsistent finding in the VCFS literature.

COMT

Similar to others [47], our data suggest that the Val allele may be associated with greater improvements across time in cognition; both groups improved yet the Val allele group improved more. This is the opposite of what is typically reported in the non-VCFS population; in both children [44] and adults [45], homozygosity for the Met allele is associated with optimal cognitive function. It has been hypothesized that the Met allele is the risk allele in VCFS by virtue of the inverted-U shape relationship between cortical dopamine signaling and cognitive functioning [96]. The inverted-U model proposes that either too little or too much D1 receptor stimulation negatively affects cognitive functioning [97]. Thus, it is hypothesized that individuals with VCFS may be predisposed to cognitive dysfunction because they have the low activity allele (Met).

Similar to others [49, 50], our results do not suggest a COMT effect on psychosis; while a higher ratio of Met allele (26%) than Val allele (15%) had significant prodromal symptoms, this difference was not statistically significant. Our results, however, are in the same general trend as those from Gothelf and colleagues [47] who found a higher prevalence of psychotic symptoms in their Met allele sample.

Our data must be considered in the context of our methodological limitations. None of the adolescents in our study met DSM-IV criteria for schizophrenia at Time 2. This may be partially explained by the relatively young age (and that many of the participants with VCFS have not yet entered the age when psychotic symptoms become more prevalent). Nonetheless, our reliance on prodromal symptoms and not full DSM-IV schizophrenia criteria may be a limitation. For example, there may not be a perfect correlation between prodromal symptoms and eventual schizophrenia. Time 3 assessments, which are already underway in our research program, will help to further determine the extent to which these Time 2 prodromal symptoms will lead to eventual schizophrenia.

Despite our limitations, these data represent one of the very few longitudinal studies which have attempted to predict psychotic symptoms in VCFS. In mid-adolescence, 20% of our VCFS sample had significant prodromal psychotic symptoms. Major depressive disorder and generalized anxiety diagnoses increased significantly in the VCFS sample. In our VCFS sample, weaker executive functioning and verbal abilities and high levels of odd/eccentric and anxious behaviors in childhood best predicted prodromal symptom levels in adolescence. The child BASC Atypicality scale and WCST Nonperseverative errors were the two best predictors of adolescent prodromal psychotic symptoms.

These data represent a good proof of concept study suggesting that the onset of prodromal psychotic symptoms is predictable. Screening for future psychosis risk may someday be possible, which would allow for preventive intervention programs to be developed. In fact, the low false positive rate suggests that, although screening will not capture all future cases, the child with VCFS who screens positive is likely to be true positives, which means that focusing clinical resources on this group could be warranted.

Acknowledgments

This work was funded by the National Institute of Mental Health by grants MH64824 and MH65481 to Wendy Kates.

In addition, the authors are grateful to the families who participated.

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Table 1

Number of Participants (Percentage of Sample) with Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) Diagnoses

Diagnosis	VCFS		Siblings		Control	
	Time 1	Time 2	Time 1	Time 2	Time 1	Time 2
Schizophrenia	0	0	0	0	0	0
Major Depressive Disorder	14 (18%)	45 (64%) ***	1 (3%)	8 (30%) *	2 (5%)	2 (8%)
Bipolar Disorder	3 (4%)	0	0	0	0	0
ANY MOOD DISORDER	17 (21%)	45 (64%)	1 (3%)	8 (30%) *	2 (5%)	2 (8%)
Panic Disorder	2 (3%)	0	0	0	0	0
Separation Anxiety Disorder	4 (5%)	4 (6%)	0	0	0	0
Simple Phobia	19 (24%)	12 (17%) *	4 (12%)	2 (7%)	2 (5%)	2 (8%)
Social Phobia	2 (3%)	5 (7%)	0	0	0	0
Generalized Anxiety Disorder	14 (18%)	19 (27%) *	3 (9%)	2 (7%)	6 (15%)	4 (16%)
Obsessive Compulsive Disorder	3 (4%)	2 (3%)	0	0	0	0
Post-traumatic stress disorder	1 (2%)	0	0	0	0	0
ANY ANXIETY DISORDER	35 (44%)	37 (53%)	6 (18%)	4 (15%)	7 (17%)	4 (16%)
Enuresis	12 (15%)	6 (9%) *	0	0	0	0
Encopresis	3 (4%)	0	0	0	0	0
Anorexia	0	0	0	0	0	0
Bulimia	0	0	0	0	0	0
ADHD	36 (45%)	29 (41%)	4 (12%)	2 (7%)	15 (38%)	8 (32%)
Oppositional Defiant Disorder	7 (9%)	14 (20%) **	0	2 (7%)	3 (8%)	4 (16%)
Conduct Disorder	0	0	0	0	0	0
Tic Disorder	0	0	0	0	0	0
Tourette's disorder	0	0	0	0	0	0
Substance Abuse	0	0	0	0	0	0
Substance Dependence	0	0	0	0	0	0

Note. VCFS = Velocardiofacial syndrome. ADHD = Attention Deficit/Hyperactivity Disorder. McNemar chi-square tests comparing Time 1 and Time 2 between groups.

* $p < .05$;

** $p < .01$;

*** $p < .001$.

Table 2

Psychological Test Performance

	Overall Model (Time By Study Group Interaction)			T1 − T2 Z-score change (p-value)		
Psychological Test	**F (2, 118)**	***p***	**eta^2**	**VCFS**	**Siblings**	**Controls**
			WISC/WAIS			
Full Scale IQ	4.24	.017	.07	−0.13 (.015)	−0.11 (.202)	+ 0.16 (.068)
Verbal Comprehension IQ	3.18	.045	.05	−0.06 (.322)	−0.24 (.016)	+ 0.11 (.262)
Perceptual Organization IQ	4.50	.005	.09	+ 0.00 (.966)	+ 0.09 (.434)	+ 0.46 (.001)
Processing Speed IQ	1.42	.243	.03	−0.30 (.001)	−0.12 (.382)	−0.05 (.706)
FDIQ	0.45	.638	.01	−0.32 (.001)	−0.37 (.007)	−0.19 (.180)
			WIAT			
Reading	3.95	.023	.08	+ 0.16 (.022)	−0.15 (.196)	−0.14 (.261)
Math	0.51	.607	.01	−0.20 (.041)	−0.01 (.936)	−0.17 (.331)
			CVLT			
List A Total	0.91	.404	.01	−0.33 (.054)	−0.60 (.034)	−0.05 (.859)
List A Trial 1	1.01	.369	.02	−0.17 (.304)	−0.54 (.041)	−0.05 (.850)
List A Trial 5	1.03	.361	.02	−0.55 (.004)	−0.85 (.007)	−0.21 (.521)
List B	0.57	.565	.01	−0.28 (.074)	−0.07 (.781)	−0.47 (.085)
List A Delay	0.69	.504	.01	−0.42 (.021)	−0.48 (.015)	−0.21 (.437)
			Visual Span			
Forward	3.56	.032	.07	−0.21 (.098)	−0.07 (.748)	+ 0.48 (.038)
Backward	2.58	.080	.05	−0.06 (.714)	+ 0.03 (.901)	+ 0.61 (.018)
			CPT – GDS			
Vigilance Omission	0.64	.529	.01	+ 0.81 (.053)	+ 0.43 (.520)	+ 1.53 (.034)
Vigilance Commission	0.39	.682	.01	+ 0.42 (.524)	−0.11 (.921)	+ 1.25 (.272)
			WCST			
Perseverative Errors	6.62	.003	.13	+ 0.77 (.001)	+ 0.70 (.004)	−0.25 (.312)
Nonperseverative Errors	1.96	.147	.04	−0.18 (.253)	+ 0.34 (.201)	−0.36 (.200)
			Tower of London			
Total Moves	1.01	.365	.02	+ 0.81 (.008)	+ 0.95 (.062)	+ 1.65 (.002)

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Note. VCFS = Velocardiofacial syndrome. WISC-III = Wechsler Intelligence Scale for Children – 3rd edition (Wechsler, 1991). WIAT-II = Wechsler Individual Achievement Test-Third edition. CVLT = California Verbal Learning Test (CVLT). GDS-CPT = Gordon Diagnostic System - Continuous Performance Test (CPT). WCST = Wisconsin Card Sorting Test. IQ = Intellectual Quotient. FDIQ = Freedom From Distractibility Intellectual Quotient.

Table 3

Parent Report of Child Behavior

	Overall Model			T1 − T2 T-score change (p-value)		
Parent Report Measure	**F (2, 112)**	***p***	**eta^2**	**VCFS**	**Siblings**	**Controls**
				BASC		
Hyperactivity	1.35	.253	.03	+ 0.89 (.554)	+ 2.72 (.307)	− 3.00 (.236)
Aggression	0.31	.734	.01	− 0.01 (.997)	− 0.78 (.708)	+ 1.40 (.478)
Conduct	1.10	.336	.02	+ 0.37 (.779)	− 3.17 (.180)	+ 1.25 (.576)
EXTERNALIZING	0.15	.862	.01	+ 0.55 (.642)	− 0.67 (.751)	− 0.20 (.920)
Anxiety	2.74	.101	.06	+ 1.84 (.276)	− 1.06 (.729)	− 3.25 (.250)
Depression	0.37	.691	.01	− 1.00 (.524)	− 0.33 (.904)	− 3.30 (.210)
Somatic	0.77	.466	.02	− 1.73 (.298)	+ 2.00 (.495)	+ 0.90 (.746)
INTERNALIZING	0.46	.634	.01	− 0.66 (.636)	+ 1.24 (.626)	− 2.05 (.381)
Atypicality	0.19	.831	.01	− 3.02 (.073)	− 1.56 (.597)	− 4.00 (.154)
Withdrawal	0.92	.402	.02	+ 1.30 (.481)	− 0.78 (.811)	− 3.50 (.259)
Attention	2.01	.140	.04	+ 1.30 (.334)	+ 2.72 (.253)	− 3.25 (.151)
TOTAL	0.92	.403	.02	− 0.25 (.860)	+ 0.65 (.801)	− 3.55 (.135)
Social Skills	1.00	.373	.02	+ 0.13 (.915)	+ 2.47 (.247)	− 1.60 (.416)
Leadership	0.10	.915	.01	+ 0.18 (.865)	+ 0.89 (.634)	− 0.25 (.888)
ADAPTIVE	0.77	.467	.02	+ 0.40 (.725)	+ 1.77 (.389)	− 1.60 (.397)

Note. VCFS = Velocardiofacial syndrome. BASC = Behavioral Assessment Scales for Children.

Table 4

Time 2 Scale of Prodromal Symptoms Descriptive Data

	VCFS	Siblings	Controls
Positive Symptoms	1.3 (2.9) ***	0.0 (0.2)	0.4 (1.2)
Negative Symptoms	2.0 (3.7) **	0.3 (0.8)	0.9 (1.7)
Disorganized Symptoms	1.0 (2.4) ***	0.1 (0.5)	0.1 (0.5)
SOPS Total	4.2 (7.7) **	0.4 (1.2)	1.3 (2.8)

Note. VCFS = Velocardiofacial syndrome.

** $p < .01$;

*** $p < .001$.

Table 5

Significant Results from Poisson Regression Predicting Time 2 Prodromal Symptoms in Velocardiofacial Syndrome Participants

Variable	z-Score	*p*
Psychological Tests		
WCST Perseverative Errors Standard Score	− 2.59	.010
Visual Span Backward	− 6.86	.000
Visual Span Forward	− 3.19	.001
Stroop Color-Word Interference T-Score	− 2.59	.010
WISC-III Processing Speed Index	− 3.67	.000
WISC-III Verbal Comprehension Index	− 3.81	.000
Behavioral/Psychiatric		
BASC Atypicality	2.82	.005
BASC Anxiety	2.79	.005
CGAS	− 4.94	.000
PAS	4.57	.000

Note. WCST = Wisconsin Card Sorting Test. WISC-III = Wechsler Intelligence Scale for Children – 3rd edition. BASC = Behavioral Assessment Scales for Children. CGAS = Clinician Rated Global Assessment Scale. PAS = Premorbid Adjustment Scale.