Schizophrenic-like neurocognitive deficits in children and adolescents with 22q11 deletion syndrome

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Abstract:

22q11.2 Deletion Syndrome (22q11DS) is the most common genetic microdeletion syndrome affecting humans. The syndrome is associated with general cognitive impairments and specific deficits in visual-spatial ability, non-verbal reasoning, and planning skills. 22q11DS is also associated with behavioral and psychiatric abnormalities, including a markedly elevated risk for schizophrenia. Research findings indicate that people with schizophrenia, as well as those identified as schizoptypic, show specific cognitive deficits in the areas of sustained attention, executive functioning, and verbal working memory. The present study examined such schizophrenic-like cognitive deficits in children and adolescents with 22q11DS (n = 26) and controls (n = 25) using a cross-sectional design. As hypothesized, 22q11DS participants exhibited deficits in intelligence, achievement, sustained attention, executive functioning, and verbal working memory compared to controls. Furthermore, deficits in attention and executive functioning were more pronounced in the 22q11DS sample relative to general cognitive impairment. These findings suggest that the same pattern of neuropsychological impairment seen in patients with schizophrenia is present in non-psychotic children identified as at-risk for the development of schizophrenia based on a known genetic risk marker. © 2006 Wiley-Liss, Inc.

Keywords: 22q11 | 22q11 deletion syndrome | schizophrenia | schizotypy | cognitive | neurocognitive | psychology

Article:

INTRODUCTION

The present study examined the relationship between Chromosome 22q11.2 Deletion Syndrome (22q11DS) and schizophrenic-like neurocognitive deficits in children and adolescents. Retrospective studies suggest that the syndrome is strongly associated with the occurrence of psychotic disorders in adulthood [Pulver et al., 1994; Papolos et al., 1996; Bassett et al., 1998; Murphy et al., 1999], and thus, represents a promising point of entry for the study of schizophrenia in a genetic high-risk sample. It is hypothesized that non-psychotic children and adolescents with 22q11DS will exhibit neurocognitive impairment consistent with deficits demonstrated by patients with schizophrenia.

22q11 DELETION SYNDROME

22q11DS, also referred to as DiGeorge Syndrome or Velo-Cardio-Facial Syndrome (VCFS), is the result of a hemizygous deletion at band 11.2 on the long arm of chromosome 22 [Shprintzen, 2000]. A variety of medical, cognitive, and psychosocial deficits have been associated with the condition [Bassett and Chow, 1999; Gerdes et al., 1999; Murphy et al., 1999; Shprintzen, 2000; Swillen et al., 2000; Bearden et al., 2004; van Amelsvoort et al., 2004; Zinkstok and vanAmelsvoort, 2005]. Cognitive deficits include learning disabilities and mild mental retardation [Eliez et al., 2000; Swillen et al., 2000; Bearden et al., 2001], and non-verbal learning deficits [Rourke, 1995; Swillen et al., 1999; Bearden et al., 2001].

22q11 Deletion Syndrome and Schizophrenia

Retrospective findings have linked 22q11DS with a markedly elevated rate of psychotic disorders such as schizophrenia and bipolar disorder [e.g., Papolos et al., 1996; Gothelf et al., 1997; Bassett et al., 1998; Yan et al., 1998; Bassett and Chow, 1999]. Murphy et al. [1999] reported that 24% of their patients with VCFS suffered from schizophrenia, and Pulver et al. [1994] reported that 31% of their sample of individuals with 22q11DS met criteria for

schizophrenia or schizoaffective disorder. These studies suggest that the risk for schizophrenia among populations with 22q11DS may be 25–30 times that of the general population. By comparison, research has not provided comparable evidence of an elevated risk for schizophrenia among individuals with other clearly identified genetic syndromes [Bassett and Chow, 1999]. Studies investigating the presence of 22q11 deletions in identified schizophrenic populations have yielded rates between 1 and 6 % [Karayiorgou et al., 1995; Yan et al., 1998; Usiskin et al., 1999; Horowitz et al., 2005]. These findings represent the strongest link to date between vulnerability to schizophrenia and a known genetic anomaly.

Schizophrenia appears to be best conceptualized as a neurodevelopmental disorder [Weinberger, 1987; Vincente and Kennedy, 1997; Andreasen, 1999], the liability for which is thought to result from a process of neural dysmaturation that arises in prenatal development and culminates in late adolescence and early adulthood [Andreasen et al., 1999]. This vulnerability may be influenced by a variety of factors including genetic inheritance and gene expression, pre- and peri-natal complications, and postnatal biopsychosocial stressors. While evidence from twin, adoption, and family studies indicates a substantial genetic contribution to this disorder, the number of genes responsible, location of these genes, and their modes of transmission are not well understood at this time. It is likely that the vulnerability to schizophrenia is influenced by a polygenic or oligogenic model of transmission that is further influenced by environmental factors. Since recent studies have established the high risk for schizophrenia in individuals with the 22q11.2 deletion, this condition may represent an etiologically specific subtype of the disorder [Gothelf et al., 1997; Bassett et al., 1998; Bassett and Chow, 1999; Murphy et al., 1999]. Alternatively, 22q11DS may provide a more general contribution toward the neuro-maldevelopment associated with vulnerability to schizophrenia.

COGNITIVE CHARACTERISTICS OF PATIENTS WITH 22qDS

Cognitive and educational abilities of children and adolescents with 22q11DS show wide variation in intelligence with a mean Full-Scale IQ around 70 [Swillen et al., 2000]. Children and adolescents with 22q11DS also tend to show a pattern of relative strengths in the areas of word knowledge, factual information, and understanding of concrete situations, and pronounced deficits in the areas of visual-spatial memory, non-verbal reasoning, and perceptual motor skills [Swillen et al., 1999, 2000; Eliez et al., 2000; Zinkstok and vanAmelsvoort,2005]. Individuals with 22q11DS continue to show deficits in visuoperceptual skills, problem-solving, and abstract reasoning in adulthood [Henry et al., 2002; van Amelsvoort et al., 2004].

Recently, interest in specific gene variations within the commonly deleted region in 22q11DS has led to findings suggesting that a functional polymorphism in the *COMT* gene predicts

cognitive performance. Additionally, similar findings in non-deleted individuals identified as at-risk for the development of schizophrenia and in non-deleted schizophrenia patients show differential cognitive performance as a function of COMT allele variations. These findings indicate that patterns of cognitive performance on prefrontally mediated tasks, as well as general cognitive decline, may be related to allele variation in COMT [Egan et al., 2001; Bilder et al., 2002; Malhotra et al., 2002; Wonodi et al., 2003; Bearden et al., 2004; Gothelf et al., 2005; Shashi et al., 2006].

Relationship Between Cognitive-Behavioral Profiles in 22q11DS and Schizophrenia

Given the increased risk of schizophrenia in patients with 22q11DS, researchers have begun to link many of the biobehavioral and neurocognitive manifestations of these two disorders. Although there is evidence of a generalized cognitive deficit in schizophrenia patients [Cornblatt and Erlenmeyer-Kimling, 1985; Saykin et al., 1994], many studies have shown deficits in specific cognitive domains in persons identified as schizophrenic or schizotypic, as well as in first degree relatives of individuals with schizophrenia [Voglmaier et al.,1997; Saykin et al., 1991; Seidman et al., 1997]. Individuals with schizophrenia tend to perform worse than comparison groups on sustained attention, executive functioning, and verbal working memory [e.g., Lenzenweger and Dworkin, 1998]. Additionally, individuals who are psychometrically identified as schizotypic show similar deficits in attention, executive functioning, and verbal working memory [Lenzenweger and Dworkin, 1998; Erlenmeyer-Kimling, 2000; Erlenmeyer-Kimling et al., 2000]. The presence of this pattern of cognitive impairment in non-psychotic individuals who have been identified as schizotypic indicates that these deficits exist in the absence of the effects of medication, hospitalization, or the catastrophic nature of the disorder itself, and supports a continuum of cognitive impairment in schizophrenic patients and in vulnerable individuals.

GOALS AND HYPOTHESES OF THE PRESENT STUDY

The goal of the present study was to examine cognitive abilities in non-psychotic children and adolescents with 22q11DS using a cross-sectional case-control design. Specifically, the aims of this study were to evaluate general cognitive ability in children and adolescents with 22q11DS, and functioning in the specific domains of sustained attention, executive functioning, and verbal working memory. These domains of functioning were selected because they have been shown to be impaired in individuals with schizophrenia, even in premorbid and prodromal stages. Furthermore, these deficits are reported in schizotypic individuals and non-psychotic relatives of

patients with schizophrenia, suggesting that they are promising markers of vulnerability for schizophrenia. It is hypothesized that, compared to controls: (a) participants with 22q11DS will exhibit deficits in the domains of sustained attention, executive functioning, and verbal working memory, (b) consistent with the established literature, participants with 22q11DS will exhibit lower IQ and achievement scores, (c) participants with 22q11DS will have increased rates of psychopathology, and (d) differences in neurocognitive functioning between the groups will be independent of differences in intelligence or diagnosis.

The purpose of the present study is construct validation as originally defined by Cronbach and Meehl [1955]. Based upon the extant literature that children with 22q11DS are at markedly elevated risk for developing schizophrenia, we hypothesize that, as a group, they should exhibit schizophrenic-like neurocognitive deficits. The value of studying at-risk individuals before they enter the age of greatest risk is threefold: it allows us to test hypotheses regarding the presence of schizophrenic-like neurocognitive deficits in an at-risk sample, it provides a baseline for longitudinal study, and it allows us to assess neurocognitive deficits relatively unaffected by the severe consequences of developing a schizophrenia-spectrum disorder.

MATERIALS AND METHODS

Participants

The sample consists of 26 patients with 22q11DS recruited through the Department of Genetics at Wake Forest University School of Medicine (WFUSM), and 25 control participants selected through recruitment within the pediatric medical genetics and general pediatrics clinics at WFUSM, as well as from area pediatric clinics and schools. The participants in the two groups were matched for sex and age (within 6 months). Participants ranged in age from 7 to 16. Groups did not differ on age at initial assessment, level of education, ethnicity, or sex. The control group exceeded the 22q11DS group on rating of parental social position [Hollingshead, 1957]. Chromosomal deletions were confirmed using fluorescence in situ hybridization. Table I presents the demographic information for the two groups. Consent was obtained from the parent or legal guardian of each participant.

Table I. Demographic Characteristics of 22q11DS and Control Groups

	22q11DS (n = 26)	Controls (n = 25)

Age (years)	9.3 (2.6)	9.7 (2.4)
Gender	39% female	48% female
Ethnicity	96% Caucasian/4% African American	96% Caucasian/4% African American
Social position[a]	38.1 (15.6)	25.5 (11.8)*
Education (years)	2.2 (2.5)	2.9 (2.1)
Global adjustment	61.7 (10.0)	72.0 (9.7)**

a Lower scores on social position indicate higher socioeconomic status.

* $P < 0.01$.

** $P < 0.001$.

A detailed family history was obtained for each participant. Potential control subjects were excluded from the study if there was a psychotic illness in a first degree family member. In the 22q11DS group, the presence of psychosis in a family member who did not have a 22q11.2 deletion served as an exclusionary criterion. The occurrence of psychotic illness in a parent affected with 22q11DS did not qualify as an exclusionary factor for children with 22q11DS.

Materials

Measures evaluating sustained attention, executive functioning, verbal memory, intelligence, and achievement were administered to all participants. Sustained attention was assessed using the Continuous Performance Test-Identical Pairs and AX Versions [CPT-IP; Cornblatt et al., 1989], executive functioning was assessed using the Wisconsin Card Sorting Test [WCST; Heaton et al., 1993], and verbal memory was assessed using the California Verbal Learning Test-Children's Version [CVLT-C; Delis et al., 1994]. Note that these constructs and measures are consistent with the recommendations of the National Institute of Mental Health Measurement and Treatment Research to Improve Cognition in Schizophrenia Initiative [NIMH-MATRICS; Kern et al., 2004].

Continuous performance test

The CPT assesses the ability to focus and sustain attention [Cornblatt et al., 1988; Nuechterlein et al., 1998]. Participants were administered four identical pairs conditions and the AX condition after receiving instructions and a practice condition. All scores are reported in terms of d′, a signal detection index which accounts for response bias. Cornblatt and Erlenmeyer-Kimling [1985] found that the CPT-IP was an effective predictor of the development of schizophrenia in a genetically at-risk sample.

The Wisconsin card sorting test

The WCST is widely used to assess executive functioning including planfulness, cognitive flexibility, and problem-solving [Chelune and Baer, 1986]. Indices reported in the present study are perseverative errors, non-perseverative errors, conceptual level response, and categories completed. Standard scores are reported for all indices, with higher scores representing better performance. Patients with schizophrenia and individuals presumed to be at risk for schizophrenia exhibit deficits on WCST performance [e.g., Goldberg and Weinberger, 1988; Gooding et al., 1999]. Additionally, recent findings by Diwadkar et al. [2006] demonstrated that adolescent offspring of schizophrenia patients made more perseverative errors on the WCST, consistent with Diforio et al. [2000], who also found elevations in perseverative errors on the WCST in schizotypal adolescents.

The California verbal learning test-children's version

The CVLT-C is a test of verbal learning and memory appropriate for children aged 5–16 years. Participants are verbally given an original list of items and a distracter list and asked to recall the items on repeated trials. The present study focused on three domains: recall, learning strategies, and recognition. While there is no literature to date examining the relationship between CVLT-C performance and psychosis-proneness in children, patients with schizophrenia exhibit impairment on the CVLT, as do adults with schizotypal personality disorder [Bergman et al., 1998; Hill et al., 2004].

Wechsler intelligence scale for children, 3rd edition and Wechsler individual achievement Test, 2nd edition

The WISC-III [Wechsler, 1991] battery consists of 10 scaled subtests that combine to yield a Verbal IQ score, a Performance IQ score, and a Full-Scale IQ score. Additionally, 2 extra subtests were administered and combined with the 10 basic subtests to yield 4 factor scores: Verbal Comprehension, Perceptual Organization, Freedom from Distractibility, and Processing Speed. The present study utilized six subtests from the WIAT-II [Wechsler, 2001] to assess

academic achievement in the domains of Broad Reading, Broad Mathematics, and spelling. Scores on the WISC-III and WIAT-II are normed to a mean of 100 and a standard deviation of 15.

Computerized diagnostic interview schedule for children

The C-DISC [Shaffer et al., 2000] is a structured interview that was administered to each participant's parent or caregiver in order to assess psychopathology in the participant. The C-DISC is based on the DSM-IV [American Psychological Association, 2001] criteria for psychological disorders, and is designed to address specific symptoms that must be evaluated in order to determine diagnostic status. The present study assessed Mood Disorders, Anxiety Disorders, Psychotic Disorders, Attention Deficit /Hyperactivity Disorder (AD/HD), Oppositional-Defiant Disorder, and Conduct Disorder.

Procedure

Participants were assessed individually at Wake Forest University Baptist Medical Center. The neurocognitive measures were administered by trained graduate students in clinical psychology under the supervision of a licensed clinical psychologist (T.R.K.). The administration of the assessment battery required approximately 4–5 hr, so the testing was broken into two or three sessions to minimize the effects of fatigue. Control participants received $50 upon the completion of the testing sessions. Additionally, all participants received reports summarizing the results of the assessments.

RESULTS

Sustained Attention, Executive Functioning, and Verbal Working Memory

Table II presents means, standard deviations, and group comparisons on the CPT, WCST, and CVLT-C. The four CPT-IP conditions (Numbers Fast, Numbers Slow, Shapes Fast, and Shapes Slow) were found to be highly correlated (coefficient alpha = 0.88). Thus, these four conditions were averaged to create a CPT-IP condition. The groups differed on the overall CPT-IP condition and the CPT-AX condition, with 22q11DS participants performing significantly worse on both tasks. In order to minimize the likelihood of Type I errors, groups were first compared on conceptually similar continuous variables from the WCST and CVLT-C using MANOVAs. Results indicated that there were significant differences between groups on the WCST, Wilkes' Lambda = 0.587, $P < 0.001$; and CVLT-C, Wilkes' Lambda = 0.545, $P < 0.001$. Individual *t*-tests

were conducted for each of the indices of interest, and revealed that the 22q11DS group performed significantly worse than the control group on perseverative errors, non-perseverative errors, percent conceptual level response, and categories completed on the WCST. Likewise, the 22q11DS group performed significantly worse than the control group on most CVLT-C indices, including recall for list A1, recall from list A1 to list A5, short delay free recall, short delay cued recall, long delay free recall, long delay cued recall, and recognition discriminability. However, there were no group differences in Semantic Clustering or Serial Clustering, which represent recall strategies.

Table II. Means and Standard Deviations of Neurocognitive Measures by Group

	22q11DS (n = 26)	Control (n = 25)	*t*-test
Continuous performance test[a]			
IP version	0.15 (0.29)	0.83 (0.62)	−4.71**
AX version	1.04 (1.00)	2.67 (1.12)	−5.38**
Wisconsin card sorting test[b]			
Perseverative errors	86.2 (9.9)	104.2 (11.8)	−5.75**
Non-perseverative errors	84.0 (16.4)	94.0 (17.8)	−2.02*
Conceptual level responses	82.6 (11.6)	99.0 (15.9)	−4.12**
Categories complete	2.58 (1.50)	4.48 (1.78)	−4.02**
California verbal learning test-children's version[c]			
List A1-5 recall	−1.00 (0.99)	0.59 (0.86)	−6.11**
List A1 recall	−0.83 (1.36)	0.74 (1.00)	−4.66**
Short delay free recall	−0.85 (1.16)	0.54 (0.97)	−4.62**
Short delay cued recall	−1.15 (1.19)	0.36 (1.06)	−4.80**
Long delay free recall	−1.15 (1.38)	0.44 (0.83)	−4.96**
Long delay cued recall	−1.04 (1.32)	0.48 (0.96)	−4.68**
Serial clustering	−0.54 (0.88)	−0.32 (0.89)	−0.88, n.s.
Semantic clustering	−0.02 (1.12)	−0.06 (0.70)	−0.72, n.s.
Recognition	−1.80 (2.19)	0.16 (0.81)	−4.39**

a Scores reported as d′.

b Scores reported as standard scores.

s Scores reported as z scores.

* $P < 0.05$.

** $P < 0.001$.

Intellectual Ability and Achievement

Table III displays means and standard deviations for the groups on the WISC-III. The control group scored significantly higher than the 22q11DS group on all intelligence variables including Full Scale IQ, Verbal IQ, Performance IQ, the four factor scores, and all subtests. Neither group exhibited a significant difference between Verbal IQ and Performance IQ, although at the individual level 20% of the 22q11DS participants and 29% of controls did so. Table IV presents means and standard deviations for the groups on the WIAT-II measure of academic achievement. The control group scored significantly higher on the Broad Mathematics Cluster, Broad Reading Cluster, and the spelling subtest.

Table III. WISC-III Means and Standard Deviations by Group

	22q11DS (n = 26)	Control (n = 25)	*t*-test
Scale scores			
Full scale IQ	70.7 (12.4)	108.9 (13.0)	−10.44*
Verbal IQ	74.0 (12.3)	108.8 (12.2)	−9.96*
Performance IQ	72.0 (12.9)	107.3 (13.8)	−9.35*
Factor scores			
Verbal comprehension	75.8 (12.69)	108.2 (12.6)	−8.81*
Perceptual organization	71.2 (13.4)	107.9 (14.2)	−9.19*
Freedom from distractibility	77.4 (14.0)	106.1 (13.5)	−6.86*
Processing speed	81.2 (15.9)	104.4 (14.9)	−4.91*

Table IV. WIAT-II Means and Standard Deviations by Group

	22q11DS (n = 26)	Control (n = 25)	*t*-test
Broad reading	82.3 (17.5)	97.2 (17.4)	−3.01*
Word reading	85.2 (15.3)	98.2 (13.9)	−3.05*
Reading comprehension	79.2 (18.7)	99.4 (17.8)	−3.86**
Pseudoword decoding	90.4 (16.9)	95.8 (17.0)	−0.99, n.s.
Broad mathematics	72.4 (16.0)	106.5 (14.6)	−7.84**
Math reasoning	74.8 (15.3)	108.3 (13.2)	−8.36**
Numerical operations	75.5 (17.8)	103.0 (14.0)	−6.04**
Spelling	82.3 (16.0)	97.1 (12.6)	−3.61*

* $P < 0.01$.
** $P < 0.001$.

In order to examine group differences between Full Scale IQ and achievement scores within the 22q11DS group, mean group achievement scores were subtracted from the mean group Full Scale IQ. Differences between IQ and achievement scores are often examined to assess learning disabilities. Learning disabilities are often identified by Full Scale IQ scores that are at least 15 point higher than achievement scores [Sattler, 2001], suggesting that a person is achieving at a lower level than would be expected based on intellectual ability. Neither group exhibited significant differences between IQ and achievement scores; however, at the individual level, two 22q11DS participants (8%) and 12 control participants (48%) exhibited learning disabilities. Learning disabilities were found in both reading and mathematics domains in the two groups of participants.

Childhood Psychological Disorders

DSM-IV diagnoses were based on the C-DISC interviews conducted with each child's parent or guardian. Significantly more participants met criteria for diagnosis in the 22q11DS group (62%) than in the control group (32%), Fisher's exact test <0.05. Forty-six percent of the 22q11DS participants and 8% of the control participants met criteria for an anxiety disorder, Fisher's exact test <0.01. The rate of AD/HD diagnoses was 35% in the 22q11DS group and 24% in the control group, although this difference did not reach statistical significance, Fisher's exact test = 0.54.

Likewise, the groups did not differ on the number of inattention or hyperactivity symptoms reported. No significant differences were found between the groups in terms of depressive pathology. Nine percent of the 22q11DS participants met criteria for Major Depression or Depression NOS, while none of the control participants met criteria for a depressive disorder, Fisher's exact test = 0.49. Despite the overall group differences in clinical diagnoses, there were no significant differences between the groups in terms of percentages of participants receiving mental health treatment (22q11DS group = 30%; control group = 28%). The groups differed on ratings of Global Assessment of Functioning [Endicott et al., 1976], with control participants functioning significantly better overall. None of the participants met criteria for a current or past psychotic disorder.

Relationship of Neurocognitive Functioning With IQ and Psychopathology

In order to account for the possible effect of general intellectual ability on the differences in neurocognitive performance, regression analyses were run partialling out variance associated with Verbal IQ and Performance IQ at the first step, and then entering group membership in at the second step. The effects of group over-and-above the effects of IQ were indicated by the semi-partial r^2 (or change in R^2) at step 2 (see Table V). Group membership continued to account for a significant portion of the variance on the CPT-IP and AX conditions. In terms of executive functioning, group membership continued to explain a significant portion of the variance on the Perseverative Errors index after including IQ in the model. After including IQ, group membership did not contribute significantly to the model in terms of any of the CVLT-C indices.

Table V. Neurocognitive Measures and Intelligence

	R^2 step 1 (VIQ, PIQ)	**Change in R^2 step 2 (group)**
Continuous performance test		
IP version	0.273^{**}	0.130^{**}
AX version	0.358^{***}	0.060^{*}
Wisconsin card sorting test		
Perseverative errors	0.317^{***}	0.111^{**}
Non-perseverative errors	0.065	0.035
Conceptual level responses	0.235^{**}	$0.054^{\dagger}$

	R^2 step 1 (anxiety)	Change in R^2 step 2 (group)
Categories complete	0.238**	0.059†
California verbal learning test-children's version		
List A1-5 recall	0.629***	0.002
List A1 recall	0.414***	0.000
Short delay free recall	0.455***	0.000
Short delay cued recall	0.529***	0.006
Long delay free recall	0.463***	0.000
Long delay cued recall	0.530***	0.010
Recognition	0.525***	0.031

* $P < 0.05$.

** $P < 0.01$.

**, *** $P < 0.001$.

† $P < 0.10$.

Anxiety and inattention may contribute to diminished performance on many of the measures administered in the present study. To determine whether anxiety disorder diagnosis affected neurocognitive performance, regression analyses were computed entering anxiety disorders at the first step and group membership at the next step (see Table VI). Group membership contributed significantly to the model after the effect of anxiety disorder diagnosis was partialled out for all neurocognitive indices except WCST non-perseverative errors. Additionally, anxiety disorders did not contribute significantly to the model on any of the neurocognitive measures except WCST non-perseverative errors. The same method was exacted using AD/HD inattention and hyperactivity symptoms at the first step. Group membership continued to contribute significantly to the model for all neurocognitive indices except WCST non-perseverative errors. There were no differences between our groups in terms of depression and the rates were very low, so comparable analyses partialing depression were not conducted. However, if differences in depressive pathology emerge in future assessments of this sample, the effects of these symptoms on cognitive performance need to be examined.

Table VI. Neurocognitive Measures, Anxiety, and AD/HD

Continuous performance test		
IP version	0.066†	0.274***
AX version	0.051	0.331***
Wisconsin card sorting test		
Perseverative errors	0.064†	0.349***
Non-perseverative errors	0.088*	0.033
Conceptual level responses	0.068†	0.202**
Categories complete	0.072†	0.190**
California verbal learning test-children's version		
List A1-5 recall	0.025	0.426***
List A1 recall	0.010	0.321***
Short delay free recall	0.021	0.292***
Short delay cued recall	0.035	0.288***
Long delay free recall	0.008	0.357***
Long delay cued recall	0.042	0.268***
Recognition	0.035	0.305***
	R^2 step 1 (AD/HD symptoms)	Change in R^2 step 2 (group)
Continuous performance test		
IP version	0.070	0.295***
AX version	0.044	0.361***
Wisconsin card sorting test		
Perseverative errors	0.032	0.390***
Non-perseverative errors	0.060	0.062†
Conceptual level responses	0.072	0.230***
Categories complete	0.066	0.221**
California verbal learning test-children's version		
List A1-5 recall	0.039	0.406***
List A1 recall	0.031	0.291***
Short delay free recall	0.006	0.297***

Short delay cued recall	0.022	0.309***
Long delay free recall	0.045	0.305***
Long delay cued recall	0.007	0.308***
Recognition	0.040	0.325***

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

† $P < 0.010$.

DISCUSSION

The present study examined neurocognitive deficits often seen in schizophrenia patients and at-risk samples in children and adolescents with 22q11DS. This design follows a long tradition of research conducted with groups presumed to be at genetic high risk for psychiatric disorders who have not yet manifested full-blown psychiatric symptoms [e.g., Erlenmeyer-Kimling, 2000]. Additionally, the rate of psychosis reported in adults with 22q11DS (25–30%) is substantially higher than the rate of psychosis reported in offspring of biological parents with schizophrenia (~10%), who have represented a common paradigm for genetic high-risk samples, suggesting that the present population is especially promising for this type of work. We believe that this is the first study to specifically report that schizophrenic-like neurocognitive deficits are more pronounced relative to intellectual functioning in non-psychotic participants with 22q11DS than control participants.

Neurocognitive Functioning

As hypothesized, the 22q11DS group performed significantly worse on measures of sustained attention, executive functioning, and verbal memory as compared to controls, and many of these findings remained even after accounting for the effects of Verbal and Performance IQ. These findings are consistent with previous reports of deficits in patients with schizophrenia and their first degree relatives, suggesting that these deficits appear prior to decompensation during premorbid and prodromal stages of illness [Nuechterlein, 1983; Cornblatt and Erlenmeyer-Kimling, 1985].

The present findings indicate that children with 22q11DS exhibit deficits in sustained attention, and that these difficulties are over and above what would be expected based on general deficit in IQ. Cornblatt et al. [1988] reported that the CPT version used in the present investigation was successful at detecting attention deficits in unaffected, at-risk offspring of persons with schizophrenia, and that it was an effective predictor of the subsequent development of schizophrenia.

In terms of executive functioning, results from the WCST indicate that participants with 22q11DS made more matching mistakes than controls and had a higher rate of perseveration, or continued use of the same sorting strategy even when it ceased being effective. Further, participants with 22q11DS scored lower on Conceptual Level Responses, which indicates a participant's understanding of the task by calculating strings of correct matches. Perseverative Errors continued to account for a significant portion of variance between groups after the effects of IQ were taken into account, indicating that the results are robust against small sample size and independent of the effects of IQ. These findings are consistent with numerous reports that patients with schizophrenia show impairments on the WCST compared to controls [e.g., Gold and Harvey, 1993; Aloia et al., 1996]. Furthermore, individuals psychometrically identified as at-risk for schizophrenia and offspring of schizophrenia patients show increased rates of perseverative errors on the WCST [Lenzenweger and Korfine, 1994; Gooding et al., 1999; Diforio et al., 2000; Diwadkar et al., 2006]. The present findings, together with previous investigations of executive functioning using the WCST, suggest that poor performance on this measure is a promising marker of risk for schizophrenia and spectrum disorders.

As was hypothesized, data from the CVLT-C indicated that participants with 22q11DS performed significantly worse than controls on recall indices. Additionally, the 22q11DS group scored significantly lower on the recognition task, indicating that these participants may have had difficulty at the encoding level. Verbal memory and verbal learning deficits have been reported in persons with schizophrenia and schizotypal personality disorder [Saykin et al., 1991; Bergman et al., 1998], as well as in the first-degree relatives of schizophrenic patients and non-psychotic adolescents identified as schizotypic, suggesting a link between verbal memory deficits and liability for schizophrenia [Lyons et al., 1995; Barrantes-Vidal et al., 1999]. Furthermore, findings suggest that patients with schizophrenia may experience encoding deficits, and that recall deficits stemming from encoding problems may be related to disorganization [Calev et al., 1983; Levin et al., 1989; Lyons et al., 1995]. The present data suggest that persons with 22q11DS experience schizophrenic-like deficits in encoding, evidencing significantly poorer discriminability on the recognition task. However, the regression findings suggest that the 22q11DS participants' deficits on verbal learning and memory were not worse than would be

expected given their impaired intellectual abilities, which is consistent with the hypothesis that 22q11DS patients have relative strengths in verbal abilities compared to non-verbal abilities.
In terms of memory strategies, the CVLT-C allows comparisons between serial clustering and semantic clustering. It is believed that semantic clustering represents a more advanced learning strategy, as it requires on-line processing as well as the manipulation of items in memory. It was expected based on lower levels of cognitive and verbal ability in persons with 22q11DS and past findings [Lyons et al.,1995] that control participants would use significantly more semantic clustering than the 22q11DS participants. However, the data did not support this expectation, showing non-significant differences between groups in terms of strategy use.
The present findings indicate that children and adolescents with 22q11DS exhibit deficits in cognitive functioning compared to control participants, and that deficits in attention and executive functioning exceed the levels that would be expected based on general intellectual functioning. These findings support previous reports of cognitive impairment in children with 22q11DS, as well as findings that these children tend to exhibit non-verbal learning deficits, as verbal learning deficits did not exceed the level that would be expected based on intellectual ability. Furthermore, the present study extends these findings by demonstrating the presence of pronounced cognitive impairment in attention and executive functioning relative to general intellectual functioning—domains in which patients with schizophrenia and people identified as at-risk show cognitive deficits.

Frontal lobe functioning

The CPT-IP, WCST, and CVLT-C assess attention, executive functioning, and working memory—higher-order cognitive processes that are mediated by the frontal lobes. Neurocognitive deficits seen in schizophrenic patients likely represent indicators of dysfunction of neuronal circuits, specifically those involved in frontal lobe functioning [Fuster, 1991, 1999; Cummings, 1995; Knight et al., 1995; Smith and Jonides, 1999; Weinberger et al., 2001; Kane and Engle, 2002; Tekin and Cummings, 2002]. In their meta-analysis examining brain-imaging studies, Davidson and Heinrichs [2003] found that the strongest group differences between schizophrenic patients and controls involved hypofrontality, or reduced frontal lobe metabolism or blood flow activity during cognitive tasks mediated by this region. The present findings of schizophrenic-like neurocognitive deficits in non-psychotic children and adolescents with 22q11DS support the examination of specific cognitive deficits as markers of risk for schizophrenia, and suggest an underlying deficit in prefrontal functioning in individuals who are at-risk.

General Cognitive Profile

The present data support previous findings regarding average IQ scores in persons with 22q11DS [e.g., Swillen et al., 2000], as this sample scored significantly below the controls and the normative mean with an average Full Scale IQ of 70.7. However, the present data did not support increased levels of learning disabilities in persons with 22q11DS. The present sample of 22q11DS children and adolescents was achieving at the level that would be expected based on Full Scale IQ scores in terms of mathematics, and was actually overachieving in the area of Broad Reading skills, with significant splits between Full Scale IQ and achievement favoring achievement.

Although these data do not support increased levels of learning disabilities in persons with 22q11DS, they do support previous findings that persons with 22q11DS show impairments resembling non-verbal learning deficits, with overall difficulties centering on mathematics and perceptual organization skills. Within the 22q11DS group, there was a small, non-significant difference between Verbal IQ and Performance IQ in favor of Verbal IQ, and the Perceptual Organization factor score was from 5 to 10 points lower than the other factor scores. Together with the achievement scores, these data support previous findings of patterns of cognitive impairment that resemble non-verbal learning deficits in persons with 22q11DS, but are inconsistent with an underlying language deficit as posited by Gerdes et al. [1999].

Children with 22q11DS may exhibit relatively small achievement deficits compared to their healthy peers while academic demands are relatively concrete. However, as demands become more abstract, children with 22q11DS experience increasing deficits relative to their classmates [Golding-Kushner et al., 1985]. Since the average level of education of children and adolescents in the present study is approximately 3 years, academic demands are likely at a concrete level. This may contribute to the relatively high level of academic achievement in the Broad Reading cluster in the present 22q11DS sample. As more data become available, evaluation of changes in cognitive functioning and academic achievement over time within the 22q11DS sample and as compared to controls will be possible, allowing further investigation into this finding.

Childhood Psychopathology

The rate of psychopathology in our control group was 32%, which, while seemingly high, appears to be consistent with epidemiological studies of the rate of psychopathology in children and adolescents [Fergussen et al., 1993; Kessler et al., 1994]. Furthermore, this rate fell within the range reported by Roberts et al. [1998] in their review of studies of the overall prevalence of childhood and adolescent disorders. While rates of psychopathology were significantly higher in the 22q11DS group than the control group, the groups did not differ significantly on rates of mental health treatment. One possibility for this concerning finding is that, given the

constellation of medical difficulties that often accompany 22q11DS, as well as intellectual deficits and subsequent educational challenges faced by these children and their families, treatment for symptoms of psychopathology may seem less urgent in terms of services. Another possibility is that anxiety symptoms, the most commonly reported symptoms in our 22q11DS sample, may seem like appropriate or understandable responses to medical difficulties, frequent medical appointments and procedures, and other difficulties faced by these children, and not viewed as separate disorders requiring services. Nevertheless, this finding is obviously concerning given the large proportion of participants who have experienced psychopathology in childhood and the significant risk of severe psychopathology in adulthood. These findings speak to the need to improve awareness of mental health issues in 22q11DS, as well over half of all children in our sample met criteria for a psychological disorder. Children with 22q11DS may benefit from psychological assessment to determine the appropriateness of mental health services, which should target current symptoms and consider prophylactic interventions to decrease the likelihood of schizophrenia and related disorders in late adolescence and early adulthood. Further investigation of childhood psychopathology in 22q11DS and risk for continued difficulties and later development of severe psychopathology is certainly warranted, including the examination of group differences in depression, especially as the participants enter adolescence.

Support for a Neurodevelopmental Model of Schizophrenia

Taken together, the present data support the presence of neurocognitive deficits in persons identified as at-risk for the development of schizophrenia based on a known genetic marker. These data are consistent with a neurodevelopmental model of schizophrenia, demonstrating the presence of deficits commonly found in persons who have decompensated into schizophrenia in a non-psychotic sample presumed to be at risk. Neural dysmaturation during development may lead to cognitive and biobehavioral impairments, many of which would be expected to manifest prior to the development of more traditional symptoms of the disorder [Andreasen, 1999]. These deficits may represent specific areas of neural dysmaturation common in schizophrenia, or may represent increased liability in and of themselves [Gooding and Iacono, 1995]. Future work will permit investigation of the predictive value of premorbid cognitive performance and other behavioral, genetic, and neural measures for psychiatric outcome. Prospective studies will attempt to examine the precise relationships among these deficits, 22q11DS, and specific risk for schizophrenia.

The present findings support the examination of cognitive functioning as an endophenotype in keeping with descriptions by Gottesman and Gould [2003] (for schizophrenia) and Waldman

[2005] (for Attention-Deficit/Hyperactivity Disorder). Specifically, cognitive processes that involve frontal lobe-mediated working memory and executive functioning may represent a distinct heritable dimension in schizophrenia [Cannon, 2005]. Endophenotypes are hypothesized to offer more immediate links to candidate genes than fully expressed clinical disorders, and may have utility in examining genetic inheritance, especially in complex diseases in which there may be multiple heritable dimensions [Cannon, 2005]. Thus, endophenotypes are presumed to provide a neurodevelopmental link between genes and manifest disorders.

Children with 22q11DS exhibit an array of cognitive, behavioral, and psychiatric difficulties that may have implications for later psychiatric outcome and adjustment. Identification of features that precede the onset of clinical symptoms is important in understanding the neurodevelopmental processes that contribute to later adjustment, as well as the development of early intervention strategies [Murphy,2005]. While the present study provides evidence for schizophrenic-like deficits in children and adolescents with 22q11DS, substantial heterogeneity of symptoms exists among individuals with this syndrome, indicating that further identification of specific risk markers for the development of psychosis in this population is needed. Continued investigation of this population, including studies of premorbid and prodromal symptoms and areas of dysfunction, may help refine our understanding of the etiological pathway(s) of schizophrenia, as well as clarify factors that further contribute to risk. Such an understanding may increase accuracy in identification of persons at risk, improving the effectiveness of prophylactic treatment efforts.

The goal of the present study was to test for hypothesized group differences in a cross-sectional design. This is a logical starting place for validating the hypothesis that non-psychotic individuals believed to be at risk for schizophrenia will demonstrate schizophrenic-like deficits—a common focus in the schizotypy literature. The present study was not an assessment of criterion validity, nor did it offer predictions about which participants will develop spectrum disorders. Such questions fall in the domain of individual differences and require longitudinal assessment. We hope to conduct longitudinal research with this sample that will allow for the measurement of individual trajectories within our at-risk group. However, a necessary precursor to longitudinal study is to establish baseline measures in the domains of interest and examine group differences.

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