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Daniel Shapiro Date

Childhood Behavior Problems and Prodromal Symptoms in Schizotypal Personality Disorder and 22q11.2 Deletion Syndrome

By

Daniel I. Shapiro
Master of Arts

Psychology

_____
Elaine F. Walker, Ph.D.
Advisor

_____
Jocelyn Bachevalier, Ph.D.
Committee Member

_____
Joseph F. Cubells, M.D., Ph.D.
Committee Member

_____
Irwin D. Waldman, Ph.D.
Committee Member

Accepted:

_____
Lisa A. Tedesco, Ph.D.
Dean of the Graduate School

_____
Date

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By

Daniel I. Shapiro
B.S., Indiana University, 2005

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An abstract of
A thesis submitted to the Faculty of the Graduate School of Emory University
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Abstract

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By Daniel I. Shapiro

Adolescents with 22q11.2 Deletion Syndrome (22q11DS) and Schizotypal Personality Disorder (SPD) are at increased genetic and behavioral risk, respectively, for the development of psychosis. No published report has directly compared these groups. Doing so can potentially shed light on the relevance of etiological subtypes in understanding the pathogenesis of schizophrenia/psychoses.

SPD, 22q11DS, and control participants were administered the Achenbach Child Behavior Checklist (CBCL) and the Structured Interview for Prodromal Syndromes (SIPS). Analyses were done with the overall sample of participants, as well as on an age-, gender-, and ethnicity-matched subsample. On the CBCL, the two high risk groups demonstrated parallel patterns of score elevations on all scales except the externalizing factor (including delinquency and aggression), where only the SPD group had higher scores than controls. On all other scales, the 22q11DS group demonstrated scores intermediate to those of the SPD and control groups. On the SIPS, both risk groups showed elevated positive, negative, and disorganized prodromal symptoms with respect to the control group, but only significantly differed from each other on positive and negative symptoms. Additionally, approximately 60% of individuals in both groups met symptom criteria for a prodromal syndrome. Results suggest that these two high risk groups are more similar than different, and that the SIPS is a valid measure of prodromal symptoms in 22q11DS.

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Schizophrenia and other psychotic disorders are complex and debilitating illnesses, affecting around 1-2% of the population. Findings from the past three decades of research on genetics and the phenomenology of Schizophrenia indicate that it is heterogeneous with respect to its etiology, course, and comorbidity (MacDonald & Shulz, 2009; Harvey & Bellack, 2009). For example, recent results from genetic studies indicate that Schizophrenia shares risk factors with other psychotic disorders, including affective psychoses (Horan et al., 2008; Maier, 2008). Thus, the identification of etiologic subtypes and risk factors that predict outcome will require more fine-grained examination of the developmental antecedents of individuals with varied risk indicators.

While the clinical onset of Schizophrenia and other psychoses is typically in the early 20's, many children and adolescents who later develop these illnesses show subthreshold, attenuated versions of psychotic symptoms. In fact, most individuals who are subsequently diagnosed with a psychotic disorder, especially Schizophrenia, experience a period of prodromal symptoms that typically begins in late adolescence/early adulthood, and lasts from 6 months to two years (McGorry et al., 1995; Cornblatt et al., 2003). Thus, the study of illness precursors and high-risk groups endeavors to shed light on the etiology of Schizophrenia and other psychoses through the longitudinal study of these pre-psychotic phenomena. Unfortunately, this type of research entails the difficult identification of individuals at heightened risk for psychosis, a difficulty exacerbated by the fact that the prodrome, itself, demonstrates phenomenologic variability (Schultze-Lutter et al., 2007).

Heightened risk for psychosis has been operationalized in a number of different ways. Some investigators identify individuals at risk for Schizophrenia based on the

presence of first degree relatives (i.e. parents, siblings, or twins) diagnosed with the disorder. Other approaches define risk status through behavioral and symptom measures that have been shown to be linked with heightened risk for subsequent psychosis. For example, individuals who manifest subclinical psychotic symptoms, such as prodromal signs or subclinical psychotic syndromes like schizotypal personality disorder, have been the focus of study (Simon et al., 2006). An alternative method focuses on at-risk genotypes that are known to be associated with psychosis. However, this method has seldom been used by investigators, because no individual gene or subset of genes has been identified that accounts for a significant proportion of the variance in risk. The one exception is the study of patients with 22q11.2 Deletion Syndrome (22q11DS).

As described in detail below, 22q11DS is a genetic disorder associated with very high rates of psychosis and Schizophrenia spectrum disorders. Though exact rates differ by study and sample size, research groups have reported rates of psychopathology in their 22q11DS samples that range from about 40% to around 80% (Baker & Skuse, 2005; Feinstein et al., 2002; Murphy et al., 1999; Arnold et al., 2001). Although only a small proportion of patients with Schizophrenia manifest 22q11DS, the rate among Schizophrenia patients is dramatically higher than that in the general population. This has alerted investigators to the possibility that research on 22q11DS may shed light on some of the genetic factors that, in general, contribute to risk for psychosis. Among the important issues to address are the phenomenological parallels between individuals with 22q11DS and those who manifest behavioral syndromes associated with risk for psychosis. The current research addresses this issue. More specifically, this study is concerned with the manifestation of behavioral problems and prodromal symptoms and

syndromes in two groups of youth deemed at risk for psychosis—namely, subjects diagnosed with 22q11DS and subjects diagnosed with schizotypal personality disorder.

'Core' Symptoms of Schizophrenia

Schizophrenia is categorized by a number of 'core' symptoms, though there is substantial variability among individuals in the phenotypic presentation. Broadly, Schizophrenia is diagnosed by the presence of positive and negative symptoms. Psychotic episodes entail one or more positive symptoms, which are loosely defined as the presence of unusual or distorted thought processes. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition—Text Revision (DSM-IV-TR) further parses positive symptoms into the "psychotic dimension," defined as distortions of thought content, including hallucinations, delusions, and paranoia; and the "disorganization dimension," which includes disturbances in the language and thought process, as well as the presence of unusual behavior.

Conversely, negative symptoms are described as the absence or diminution of normal function. Included in this category are flattening of outward or experienced affect, deficits in or amotivation toward social and vocational functioning, anhedonia, and poverty of speech and thought. These two symptom dimensions are thought to be somewhat orthogonal and to reflect different underlying mechanisms.

Many patients with Schizophrenia also show cognitive dysfunction. While deficits are not always seen in the same domain, impairment on tests of verbal memory and fluency (Gur et al., 2007), executive function (Silver et al., 2003), sustained attention (Birkett et al., 2007), and abilities measured in tests of IQ, such as the Wechsler Adult

Intelligence Scales (Allen et al., 2001; Reichenberg et al., 2006; Ott et al., 1998), are commonly observed. Thus, it has been proposed that impairments in cognition also comprise a 'core' feature of the illness.

The Prodrome to Psychosis

The prodrome to psychosis is a period of functional decline and gradual onset of subclinical symptoms that can last from a few months to several years (Corcoran et al., 2003). Both retrospective and prospective studies have been conducted on this period, and the results have shed light on the nature and course of the prodromal period: It entails attenuated positive symptoms, as well as negative and affective symptoms (Cornblatt et al., 2003), and often diagnosable depression (Lee et al., 2008). Within the past decade, researchers have developed standardized diagnostic interview procedures for diagnosing the prodrome and rating the severity of various symptom dimensions (ex: Prodromal Questionnaire; Loewy et al., 2005; SIPS/SOPS: McGlashan et al., 2001). Individuals who meet criteria for the prodrome, based on these measures, show a rate of conversion to Axis I psychosis that varies from 25 to 40% (Yung et al., 2003, Cannon et al., 2008).

Noteworthy among measures of the prodrome is the Structured Interview for Prodromal Syndromes (SIPS). The SIPS contains an instrument, the Scale of Prodromal Symptoms (SOPS), which rates the severity of four symptom domains; positive, negative, disorganized, and general. The positive symptoms rated by the SOPS include unusual sensory experiences and ideations that are atypical and cause distress for the individual, but do not meet criteria for clinical hallucinations, delusions, or thought disorder. These

symptom ratings are used to determine whether the individual meets criteria for one or more of three prodromal syndromes.

Using this instrument, researchers have found a conversion rate to Axis I psychosis that is about 30% within two years, though some studies have reported rates up to 50% (Miller et al., 2003; Yung et al., 2003; Lemos et al., 2006). Investigators are now focusing their efforts on improving the prediction algorithm by weighting symptom ratings and adding measures so that specificity and positive predictive power are enhanced (Cannon et al., 2008). This is considered the next critical step toward controlled studies of preventive intervention, which have been shown to improve prognosis of at-risk individuals (Nordentoft et al., 2006).

Schizotypal Personality Disorder as a high-risk group

Schizophrenia is posited to exist on a spectrum with acute illness on one end and less severe behavioral dysfunction, such as DSM-IV cluster A Schizotypal Personality Disorder (SPD) and schizotypy on the other. In fact, the defining criteria for the SPD syndrome were based on findings from research on the biological relatives of Schizophrenia patients (Kendler et al., 1981; Webb & Levinson, 1993; Kendler et al., 1995). These family studies revealed that biological relatives were more likely than controls to manifest both subclinical positive and negative signs of Schizophrenia. To qualify for a DSM diagnosis of SPD, an individual must show a pattern of social and interpersonal deficits together with a combination of ideas of reference, odd beliefs, unusual perceptual experiences, odd thinking, paranoia, inappropriate affect, odd behaviors, and social anxiety (Diagnostic and Statistical Manual of Mental Disorders-IV-

TR). In addition to its genetic link with Schizophrenia, SPD is also developmentally linked. Individuals with SPD show an eventual rate of Schizophrenia and other psychoses that is much higher than the population base rate (Cadenhead & Braff, 2001), though estimated rates differ by sample size and composition. For example, Asarnow (2005) found that 75-92% of her SPD sample developed Schizophrenia over 3-year follow-ups, while Mittal et al. (2008) found a conversion rate of 25%. Moreover, substantial proportions (50 to 70%) of individuals who meet diagnostic criteria for SPD also meet criteria for the prodrome (Woods et al., 2009). Thus, these conditions are posited to exist on a continuum with Schizophrenia, and it is generally assumed that they share some genetic and environmental determinants (Kendler et al., 1995).

Cognitive abnormalities in SPD

Cognitive impairments are a central feature of Schizophrenia. Just as individuals with SPD have been characterized as having subthreshold psychotic symptoms, they have also been investigated to determine whether cognitive impairments often seen in Schizophrenia also manifest in SPD. These investigations have resulted in somewhat inconsistent findings, likely due to the fact that effect sizes are not large and many studies have relatively small sample sizes. For example, findings on general impairment in cognitive ability, as measured by IQ, seem equivocal. However, agreement on a few areas of specific cognitive dysfunction does emerge. Particularly, impaired performance on vocabulary tasks (Dickey et al., 2005) and verbal memory/learning (Bergman et al., 1998; Voglmaier et al., 2000), working memory and executive function (Diforio et al., 2000; McClure et al., 2008; Trestman et al., 1995), attention/concentration (Cadenhead et

al., 1999; Weiser et al., 2003; Moriearty, 2003), and visual and auditory episodic memory (McClure et al., 2007; Mitropoulou et al., 2002) have consistently been found in individuals with SPD. Moreover, individuals with SPD and more acute cognitive deficits have been found to have more numerous and severe psychotic symptoms—particularly negative symptoms (Trotman et al., 2006; Cannon et al., 1994). All of these are domains in which individuals with Schizophrenia also show deficits, and studies that include a healthy comparison group typically find that the performance of individuals with SPD is intermediate to that of controls and probands. To summarize, the literature on cognition in SPD is well characterized by Voglmaier and colleagues (2005), who describe "mild, general decrements in performance in most cognitive domains." Thus, the cognitive profile in SPD appears to be qualitatively similar to that in Schizophrenia, but with milder dysfunction. These results suggest phenomenological and, perhaps, etiological overlap between SPD and Schizophrenia.

Brain Abnormalities in SPD

Just as the cognitive profile in SPD is similar to that in Schizophrenia, it is suggested that similar brain abnormalities exist in both groups. However, this comparison is obfuscated by the fact that few consistent imaging results appear in the SPD literature. Perhaps the two most salient findings are of enlarged cerebral ventricles (Siever et al., 1995), and reduced temporal gray matter (Downhill et al., 2001), mirroring findings in Schizophrenia cohorts. Additionally, work on this topic by Dickey and colleagues, including a meta-analysis (1999; 2002), identified abnormalities in the superior temporal gyrus, parahippocampus, temporal horn region of the lateral ventricles,

corpus callosum, thalamus, and septum pellucidum. These authors, along with Siever & Davis (2004), show that, in contrast to individuals with Schizophrenia, those with SPD have *relatively* preserved medial temporal and frontal lobe volumes. Hazlett et al. (2008) compared these two groups to a control group and came to a similar conclusion, but still found moderate reductions in frontal and temporal gray matter in SPD when compared to controls.

Behavioral problems in youth with SPD

There is a relative paucity of studies on concurrent behavioral problems in SPD youth. However, one study using the Child Behavior Checklist (CBCL) found elevated scores on the Anxious/Depressed, Withdrawn, Somatic Complaints, Delinquency, Social Problems, Thought Problems, and Externalizing Problems scales in at least 63% of their sample of youth with SPD (Meyer et al., 2005). Overall, 93% of this sample had elevated scores on the Internalizing subscale. With the exception of high delinquency scores, these results make intuitive sense, given the diagnostic criteria for SPD. The three highest CBCL factor scores for the group were anxious/depressed, withdrawn, and somatic complaints, respectively. The current study will use the CBCL to assess behavioral characteristics in both SPD and 22q11DS youth. The advantage of this approach is that the CBCL represents a broadband behavioral assessment and thus, should be sensitive to behavior in many domains.

22q11.2 Deletion Syndrome as a high-risk group

22q11DS is the second most common genetic abnormality syndrome, second only to Down's syndrome (Bassett & Chow, 1999), affecting approximately 1 in 4000 live births.[1] It is caused by an interstitial deletion of a segment on the long arm of the 22nd chromosome. This deletion is sporadic in most instances (Swillen et al., 1999), but is transmitted as an autosomal dominant trait in 10-28% of cases (Goldberg et al., 1993; Ryan et al., 1997 *cited from Gothelf et al., 1999).* In approximately 87% of cases, this deletion is 3 megabases (mB) in size, though about 8% of individuals have a 1.5 mB nested deletion, 4% have one of two other nested deletions, and the remaining 1% have unique deletions (Ivanov et al., 2003).

Regardless of which deletion individuals have, those with 22q11DS have a risk of developing Schizophrenia that is roughly 25-30 times higher than that in the general population (Murphy, 2002; Williams & Owen, 2004). Thus, it is posited that a gene or genes mapping to the 22q11.2 chromosomal region is directly or indirectly associated with the development of Schizophrenia. As described below, one gene in this region, the Catechol-o-methyl transferace (COMT) gene, has been found to be associated with risk for psychosis and cognitive dysfunction (Egan et al., 2001). Therefore, in the current study, a group of children and adolescents with 22q11DS is used as a group at genetically high risk for developing Schizophrenia.

A number of theories have been proposed regarding the mechanisms involved in 22q11DS and its myriad phenotypic manifestations. In general, it is assumed that the effects of the deletion appear during embryonic development—Maynard et al. (2002)

[1] While this is the most commonly accepted prevalence rate, estimates have varied some by study (i.e. Botto et al., 2003 found the prevalence to be 1 in 5,950 live births)

point out that most duplication/deletion syndromes, like 22q11DS, first affect fetal development, impinging on embryonic tissues that later form many different mature structures. Most often impacted are craniofacial structures, limbs, and the heart. In the case of 22q11DS, this process is thought to result from a haploinsufficiency (reduced gene dosage) of genes important to early development that map to the deleted area of chromosome 22. Specifically, multiple gene deletions/disruptions are thought to result in abnormal neural crest cell migration (Bassett & Chow, 1999; Mansour et al., 1987), leading to the subtle malformation of many body systems and organs. These neural-crest-derived cells are particularly important in the development of the conotruncal region of the heart, the thalamus, parathyroid glands, palate, and forebrain (Murphy & Owen, 2001; Maynard et al., 2001), all systems often affected in 22q11DS.

Genes in the 22q11.2 region.

A number of specific gene markers mapping to the 22q11.2 region have been implicated in the relation between the deletion and its various phenotypes (including mental illness and Schizophrenia). Specifically, a few studies have implicated the *DGCR2* gene (Shifman et al., 2006), and the *TBX1* gene (Ma et al., 2007), both on the 22q11.2 region, as being associated with the development of Schizophrenia. Most notably, though, the Catechol-o-methyl transferace (COMT) gene is also located in the 22q11.2 region. This gene codes for the production of an enzyme that affects the degradation of catecholamine neurotransmitters in predominantly prefrontal areas of the brain. As a result, different COMT genotypes are associated with different levels of prefrontal dopamine (with met/met seen as the low COMT activity and high dopamine

polymorphism, val/val as the high activity polymorphism, and val/met as intermediate). Specific COMT polymorphisms have been implicated as risk genes for the development of Schizophrenia (Egan et al., 2001), Bipolar Disorder (Shifman et al., 2004; Berrettini, 2000), as well as a more general risk factor for the development of psychopathology, broadly defined. As a result, it is posited that dopamine and the regulation thereof is involved with the development of Schizophrenia and other psychopathology.

As would be predicted by the location of the COMT gene in the 22q11.2 region, abnormal dopamine regulation is also seen in 22q11DS. Boot and colleagues (2008) found that individuals with 22q11DS have higher levels of baseline plasma dopamine, disrupted dopaminergic regulation, as well as a high incidence of psychopathology. Additionally, prefrontal dopamine is also important in learning/memory and executive function tasks, all of which are affected in both Schizophrenia spectrum disorders and 22q11DS (Silver et al., 2003; Gur et al., 2007; Birkett et al., 2007). Thus, it is plausible that a deletion at the COMT locus plays a role in the signs and symptoms seen in 22q11DS, as well as the high rates of psychopathology observed.

Researchers are also investigating other genes mapping to the 22q11.2 region for their possible contributions to the different phenotypes seen in 22q11DS. Though an in-depth summary of the genetic mechanisms in 22q11DS is beyond the scope of this paper, good reviews may be found in Maynard et al., 2002 and Amati et al., 2007. In brief, Amati and colleagues found seven genes (including COMT) mapping to the 22q11.2 chromosomal region that are active during development in the mouse. *Foxc2*, *Pax3*, and *Hoxa1* are all expressed throughout development. *Pax3* is involved in the formation of the muscular, nervous, and cardiovascular systems (Goulding et al., 1991); *Hoxa1* affects

the migration of neural crest cells; and *Foxc2* affects aspects of the formation of the head, heart, blood vessels, and lymphatic system. Amati and colleagues also mention 3 other genes, *Tsk1*, *Usp18*, and *Txnrd2*, which are expressed slightly later in fetal development, but are important for both embryonic growth and a variety of later cellular processes. Finally, they cite the *Cldn5* gene, also mapping to the 22q11.2 region, as important in heart development.

In addition to structural development, many of the genes on the 22q11.2 chromosomal region are involved with regulation of gene expression. Maynard and colleagues (2002) point to four different transcription factor genes (*HIRA*, *Tbx1*, *E2F6*, and *GSCL*) in the 22q11.2 region that code for proteins that regulate gene expression. This suggests that some phenotypic manifestations in 22q11DS could result from genes in the 22q11.2 region that interact with and modulate the expression of genes in other regions. This group also implicates genes in the region as involved with the cell cycle, the manufacturing of cell adhesion proteins, and the synthesis of enzymes and regulation of metabolic processes (e.g. COMT). They also point to a number of non-functional genes. Finally, a number of the 40-50 genes that reside on the 22q11.2 region are, as of yet, uncharacterized. Thus, genes mapping to the 22q11.2 chromosomal region appear to be involved in a multitude of cellular, organ, and system functions.

Phenotypic Variation in 22q11DS

22q11DS is associated with a multitude of physical, cognitive, behavioral, motor, and psychiatric phenotypes. In fact, different groupings of symptoms have been given different syndrome names, many of which were coined before the underlying genetic

deletion had been elucidated. Such names for 22q11DS include Velo-Cardio-Facial Syndrome (VCFS), DiGeorge Syndrome, Shprintzen Syndrome, Conotruncal Anomaly Face Syndrome, Caylor Syndrome, Opitz GBBB syndrome (Arinami et al., 2006), and CATCH22 (cardiac abnormality, abnormal face, t cell deficits, cleft palate, and hypocalcaemia). However, to date, associations between the size of the deletion and individual symptom profiles have not been identified. The following section describes some of the characteristics most often observed in those diagnosed with 22q11DS.

Physical Abnormalities in 22q11DS

Perhaps the most heterogeneous in individuals with 22q11DS are the physical and body system anomalies. Over 180 different physical abnormalities have been noted in nearly every human system and organ (Zinkstok & van Amelsvoort, 2005), though there are neither obligatory findings nor universally characteristic features. Fairly common are differences in facial features, like bulbous nasal tip, prominent nasal root, narrow and flat cheeks, small mouth, and receding chin (Shprintzen et al., 1978). Also prevalent are malformations of the limbs (Maynard et al., 2002), cardiac and respiratory systems, and speech production organs. Cleft palate, immunodeficiency, and hypothyroidism are also frequently observed. As a result of these physical signs, individuals identified as having 22q11DS often have long histories of surgeries, doctor visits, speech therapy, and hospitalizations. It is through these doctor visits, or a history of 22q11DS in the family, that most diagnoses are made (Sprintzen, 2000). However, because most individuals with 22q11DS do not have outward physical anomalies, many individuals with the syndrome do not get diagnosed as children. Further, it is possible that individuals with

the most severe impairments do not survive into adulthood. Thus, our phenotypic picture of the true concomitants of the 22q11.2 deletion may be incomplete or may be based on a less severe phenotype (Murphy & Owen, 2001).

Structural abnormalities have also been reported in the brains of individuals diagnosed with 22q11DS. In a review of the imaging literature, Zinkstok et al. (2005) highlight the most consistent findings as midline defects, structural alterations in the cerebellum and frontal lobe, as well as specific decreases in grey matter volumes in the parietal and temporal areas. More broadly, a number of studies have found decreases in total brain volume in children with 22q11DS (Eliez et al., 2000; Simon et al., 2005; Bearden et al., 2004) ranging from 4.3% to 11%, with reductions in both grey and white matter. Beyond this, more specific alterations in brain structure have been linked to cognitive and psychiatric phenotypes (e.g. cingulate gyrus, executive function, and psychotic symptoms: Dufour et al., 2008). It is worth noting that many of these findings overlap with similar results in the Schizophrenia literature.

Finally, in a longitudinal study of children/adolescents with 22q11DS and age matched controls, Gothelf et al. (2007b) found evidence for different maturational changes in the brains of these two groups. Specifically, they found a greater increase in cranial and cerebellar white and gray matter, superior temporal gyrus, and caudate nucleus volumes in those with the deletion. They also found a greater decrease in amygdala volumes between childhood and late adolescence or adulthood in these participants compared to non-disordered controls. This is compared with the finding of an increased cerebral white to gray matter ratio, decrease in caudate volume, and no change in amygdala volume over the same period in the control group. The authors

suggest that these differences reflect aberrant brain maturation and propose that they may result from a lag in the pruning of temporal and caudate gray matter. These findings are interesting given the aforementioned finding of *decreases* in temporal gray matter in Schizophrenia and SPD (e.g. Dickey et al., 1999).

Cognitive Abnormalities in 22q11DS

The cognitive profiles of individuals diagnosed with 22q11DS are much more homogenous than their physical profiles and are marked by a number of significant deficits. The most frequent finding is a deficit in broad intellectual ability, with impairments ranging from borderline to moderate. However, many children have average IQs and mental retardation is not often described (Zinkstok et al., 2005). Within their full scale IQ scores, a pattern of higher Verbal than Performance IQ is often found, leading some to relate the cognitive profile in 22q11DS to those seen in Nonverbal Learning Disorders (Niklasson et al., 2005; Van Amelsvoort et al., 2004b; Swillen et al., 1999.; Oskarsdottir et al., 2005; Lajiness-O'Neill). Robust impairments in executive function, planning, visual attention, nonverbal reasoning, and sensorimotor abilities are often reported and likely contribute to this discrepancy (Kiley-Brabeck & Sobin, 2006; Zinkstok et al., 2005). Also consistently reported is poor performance on tests of math, pragmatics, and sustained attention, as are low academic achievement scores (Arnold et al., 2001). While the specific causes of these cognitive deficits are not well understood, it is likely that the aforementioned structural brain abnormalities play a role.

A few studies have proposed that the previously described findings in specific cognitive domains in 22q11DS are due to generally low intellectual ability, rather than to

specific effects of the deletion. To address this possibility, a number of studies have been carried out in which 22q11DS individuals were compared with IQ-matched controls. For example, Henry et al. (2002) carried out a study in which individuals with the deletion were matched with control participants on IQ, age, and gender. They found that 22q11DS individuals still demonstrated impairments in visuo-perceptual ability and executive function (problem solving, planning, and abstract thinking). Further, two studies have found lower mean IQs in VCFS individuals with a familial deletion when compared to those with a de novo deletion (Swillen et al., 1997; Gerdes et al., 1999). Thus, it would appear that genes on the 22q11.2 region do play a role in the pattern of intellectual difficulties seen in the deletion syndrome.

Interestingly, many of the cognitive findings in 22q11DS parallel those in Schizophrenia and SPD. Analyzing the literature on Schizophrenia, Snitz and colleagues (2006) recently identified executive function, working memory tasks, and attention regulation tasks as potential intermediate phenotypes of genes involved in Schizophrenia. As previously mentioned, attenuated findings in the same domains are typically found in SPD. The fact that these deficits are also present in 22q11DS lends further support to the idea that 22q11DS and Schizophrenia may share some etiologic factors.

Motoric Abnormalities in 22q11DS

Individuals with 22q11DS also typically show developmental and motor delays. Often, motoric milestones, like crawling and walking (Swillen et al., 1997; 1999; Oskarsdottir et al., 2005) and the onset of speech and language (Shprintzen, 2000), are reached late. The frequent presence of hypotonia (Oskarsdottir et al., 2005; Swillen et

al., 1999) often leads to additional motor problems. Difficulties with coordination, balance, and manual dexterity are nearly ubiquitous findings in the literature (Swillen et al., 1999; Van Aken et al., 2007; Sobin et al., 2006; Chow et al., 2006) and cannot be explained by heart defects or behavioral features (Swillen et al., 2005). Signs of subtle neuromotor problems have also been found in retrospective studies of individuals with Schizophrenia, lending additional support to the notion that the etiology of 22q11DS and Schizophrenia overlap (Walker & Lewine, 1990; Walker et al., 1994).

Behavioral Abnormalities in 22q11DS

In an early observational study, Golding-Kushner et al. (1985) described a behavioral picture in 22q11DS borne out in subsequent quantitative studies. According to their observations, children with 22q11DS exhibit social withdrawal, anxiety, shyness, and impulsivity problems, as well as poor attention and concentration. These problems are compounded by frequent troubles in expressive language caused by physical malformations of the face and speech production organs (Shprintzen, 2000), as well as by social and academic delays caused by health-related absences from school and other cognitive difficulties.

Subsequent research using the CBCL has quantitatively supported these observations. For example, Heineman-de Boer and colleagues (1999) administered the CBCL to 40 individuals with VCFS and an age-matched control group with craniofacial anomalies, all between the ages of 4 and 18. They found that the VCFS group had more behavior problems than the control group, with an average T-score in the clinically significant range (above 60 for this study). Specifically, they found elevated T-scores in

the total problems and internalizing factors, reflecting clinically significant withdrawn, social problems, thought problems, and attention problem scores. Another study conducted by Lajiness-O'Neill et al. (2006) found similar results. They compared a group of 14 children with VCFS with 8 of their discordant siblings and found that the proband group had higher social concerns, thought problems, and attention problems scores, all of which had t-scores of over 65. Nikklasson and her co-investigators (2005) also found clinically significant scores on the attention problems subscale in 30 children with 22q11DS, but did not report on any of the other subscale or factor scores. Similarly, Swillen et al. (1997) found significant behavioral problems in the social problems, attention problems, thought problems, withdrawn behaviors, and anxiety subscales in 37 children diagnosed with VCFS. Bearden et al. (2004) followed these findings up by looking for associations between these subscales and brain abnormalities. They found that reduced temporal gray matter was associated with increased thought problems scores in their sample of 13 children with 22q11DS.

In a different design, Feinstein and co-authors (2002) matched 28 children with VCFS with 29 age and IQ matched control participants. They found differences between the two groups on each of the following CBCL factors: externalizing problems, delinquency, and aggressive behavior, though social and attention problems were both also in the clinically significant range (t-scores above 65) for the VCFS group. In another study, Swillen and colleagues (2005) matched participants to account for conotruncal heart defects (VCFS =11, control = 19) and found differences on only the withdrawn subscale.

A number of studies have investigated the behavioral profiles of individuals with 22q11DS using standardized scales other than the CBCL. For example, Karen Kiley-Brabeck and Christina Sobin,(2006) found that 52 children with 22q11DS had lower (worse) Social Skills Rating System scores for the social skills subscales of cooperation, assertion, responsibility, and self-control than 26 control siblings. These findings relate directly to the social problems subscale of the CBCL. In another paper, Baker and Skuse (2005) administered the Child and Adolescent Psychiatric Assessment scale and Premorbid Adjustment Scale to 25 adolescents/young adults (ages 13-25) with 22q11DS and 25 age- and IQ-matched controls. They found that the 22q11DS individuals showed more abnormal premorbid sociability/isolation, peer relations, adaptation to school, and poverty of interest scale scores. Nearly half of these individuals reported transient psychotic experiences and showed inattention symptoms, anxiety, and depressive mood. These findings relate directly to the social, withdrawal, attention, internalizing, and thought problems subscales of the CBCL.

To summarize, past studies using behavioral rating scales indicate that children with 22q11DS often show elevated scores on withdrawn, social concerns, thought problems, attention problems, and internalizing CBCL scores. Externalizing problems, delinquency, and aggressiveness related behaviors have also been observed.

It is noteworthy that these findings in 22q11DS bear some resemblance to findings in other groups at high risk for Schizophrenia. For example, in a longitudinal high risk study, Welham et al. (2008) assessed a birth cohort of 3801 individuals in Australia with the CBCL at ages 5 and 14, then assessed for non-affective psychoses at age 21. They found that individuals who developed Schizophrenia (n=60) had higher

'Total' behavior problems, as well as higher Aggression, Social, Attention, and Thought problems scores on the CBCL at age 5. These 60 individuals also had higher social, attention, and delinquency scores at age 14. Further, they found that presence of hallucinations predicted psychosis when present at age 14. They also found that high total problems scores at both years 5 and 14 in boys, and high or increasing social, attention and thought problems scores between ages 5 and 14 in both genders were associated with increased risk for psychosis at age 21. Thus, the CBCL behavior problem factors that are found to be elevated in pre-Schizophrenia children are similar to those observed in children with 22q11DS.

Nonpsychotic Psychopathology in 22q11DS

Adding to the complex phenotypic picture in 22q11DS are high rates of a variety of nonpyschotic psychiatric disorders. Arnold et al. (2001) reported that 60% of their 22q11DS sample met diagnostic criteria for an axis I disorder. While most studies report similarly high numbers, the rates of specific diagnoses vary depending on the method of patient ascertainment and measurement. Some of the psychiatric diagnoses are intimately tied to the aforementioned behavioral signs of 22q11DS. For example, the rates of anxiety and mood disorders are 2-3 times those seen in the general population (Murphy, 2002). Also, many reports cite high incidences of ADHD (43%: Niklasson et al., 2005 48%: Baker & Skuse; 36%: Papolos et al., 1996), analogous to the earlier reported findings of problems with sustained attention, and internalizing and externalizing issues. Papolos et al., (1996) estimated the prevalence of mood disorders in 22q11DS to be 52%, though studies vary substantially in the numbers they report. For example, Arnold et al.

(2001) reported a 40% incidence in their 22q11DS sample, while Murphy & Owen (1997) reported a 15.5% incidence of mood disorders in their sample. Some diagnoses also reflect the aforementioned cognitive deficits seen in 22q11DS, such that Swillen et al. (1999) estimated the rate of Nonverbal Learning Disability to be 55%. Developmental disorders are also common, as are anxiety disorders (71% of the Gothelf et al., (2007) sample), and approximately 11% are diagnosed with Autistic spectrum disorders (Fine et al., 2005, cited from Arinami, 2006). Most relevant for the present investigation is the very high rate of psychosis and Schizophrenia in 22q11DS.

22q11DS and Schizophrenia Symptoms

The incidence of Schizophrenia in the general population is roughly 1% (Torrey, 1987; Perala et al., 2007; McGrath et al., 2008). However, in individuals diagnosed with 22q11DS, the rate of Schizophrenia is estimated at between 25 and 30%, while psychosis, broadly defined, has been observed in between 30 and 50% of individuals (Shprintzen et al., 1992; Murphy et al., 1999; Gothelf et al., 2007; Pulver et al., 1994). Conversely, those with a 22q11.2 deletion make up a small proportion of all individuals with Schizophrenia; only .33-2% of individuals with a diagnosis of Schizophrenia have been found to have the 22q11.2 deletion (Ivanov et al., 2003; Karayiorgou et al., 1995; Horowitz et al., 2005; Goodship et al., 1998). Nonetheless, this is a much higher rate than in the general population, in that only .00025 of randomly sampled healthy subjects have the 22q11.2 deletion.

Additionally, a few studies have investigated subthreshold positive symptoms in youth with 22q11DS. Baker & Skuse (2005), for example, found that nearly half of their

22q11DS sample experienced “transient psychotic experiences” and Gothelf et al. (2007) reported an increased incidence of psychotic symptoms in their sample. Similarly, Debanne et al. (2006) found that 28% of their sample of children and adolescents with 22q11DS had psychotic symptoms, and that these individuals also had increased CBCL anxious/depressed and withdrawn subscale scores.

Thus, given the high rate of Schizophrenia symptoms and diagnoses in 22q11DS, it has been suggested that it may represent an etiologic subgroup of Schizophrenia patients (e.g. Bassett & Chow, 1999; Chow et al., 2006). In this connection, it is noteworthy that while many genes have been implicated as risk factors for Schizophrenia and other psychotic disorders, all of these candidate genes explain only a small amount of variance (3-4%) in diagnostic outcome (Egan et al., 2001; Saetre et al., 2008; Lewis et al., 2003; Harrison & Weinberger, 2005), or have odds ratios that are considered small to moderate in studies that investigate allele frequencies in proband v. non-proband groups (Moskvina et al., 2009; Owen et al., 2005). The fact that the presence of the 22q11.2 deletion increases risk of developing Schizophrenia to roughly 25-30%, and that positive symptoms are observed in many who do not develop diagnosable psychosis, suggests that multiple genes in this region may be involved. It is possible that Schizophrenia, as it develops in 22q11DS, is a unique syndrome, with a phenotype similar to other forms of Schizophrenia, but distinct genetic mechanisms. Comparative studies of 22q11DS Schizophrenia patients (22q-SZ) with non 22q11DS Schizophrenia patients (non-22q-SZ), as well comparative studies of 22q11DS patients without psychosis with non-22q-SZ, can help address this issue.

A number of papers have been published that describe similar deficits in non-22q-SZ and non-psychotic patients with 22q11DS. For example, one of the most robust findings in the Schizophrenia literature is of impaired sensory-gating, measured by attenuated prepulse inhibition (PPI), which is often seen as an endophenotype of Schizophrenia risk genes (Geyer et al., 2001; Braff & Light, 2005; Kumari et al., 2005). Sobin et al. (2005) found that individuals with 22q11DS had reduced PPI when compared to their own siblings discordant for the 22q11.2 deletion, possibly due to a gene mapping to the 22q11.2 chromosomal region (Gogos et al., 1999). Further, Lewandowski and colleagues (2007) found what they called "Schizophrenic-like neurocognitive deficits" in nonpsychotic children with 22q11DS. These included deficits in intelligence, achievement, sustained attention, executive functioning, and verbal working memory, leading the authors to conclude that individuals with Schizophrenia and non-psychotic 22q11DS children shared similar cognitive deficits. Evidence that 22q11DS and non-22qSZ are similar suggests that they may share some genetic factors.

In a similar vein, Murphy (2002) points out in a review article that findings of enlarged ventricles, reduced total brain volume, and midline brain abnormalities seen in 22q11DS have also been observed in Schizophrenia. Some of these same structural abnormalities have also been found in individuals with SPD (Siever et al., 1995; Dickey et al., 2007). Though structural findings in all three populations vary somewhat by study (i.e. Gothelf et al., 2007), there is ample overlap to suggest that patients with 22q11DS have some of the same structural brain abnormalities observed in Schizophrenia and other spectrum disorders. Also, as is the case in Schizophrenia, greater volumetric reductions have been shown to be associated with symptom severity in 22q11DS. In a recent

imaging study, Bearden et al. (2004) found that reductions in temporal grey matter were associated with increased Thought Problems scores on the CBCL in 22q11DS subjects.

22q11DS patients with and without Schizophrenia

Several studies have compared 22q11DS patients with no psychopathology to those with Schizophrenia; most of this work has investigated cognition. In this domain, the findings indicate that 22q11DS patients with Schizophrenia show worse performance on certain cognitive tasks when compared to nonpsychotic 22q11DS subjects. These areas of deficit tend to correspond with those generally impaired in Schizophrenia. For example, Chow et al. (2006) found that individuals with 22q-SZ had lower IQ's, more impaired motor skills, poorer verbal learning, and impaired social cognition when compared with nonpsychotic 22q11DS patients. Along these same lines, Van Amelsvoort et al. (2004b) found that patients with 22q-SZ performed worse on a number of executive function and attention tasks than an age- and IQ-matched sample of nonpsychotic 22q11DS patients.

Differences in brain morphology have also been found between 22q11DS patients with and without psychosis. Van Amelsvoort and co-authors (2004a) reported that individuals with 22q11DS that developed Schizophrenia differed in brain volume from those that did not. Specifically, there were reductions in whole brain volume, as well as white matter, in those who developed Schizophrenia, though both groups had reduced cerebellar volumes when compared to controls. Therefore, it seems that 22q11DS individuals who develop Schizophrenia have more severe impairment in certain cognitive

functions and brain regions, many of which parallel differences between healthy controls and those with Schizophrenia.

22q11DS with Schizophrenia versus Schizophrenia without 22q11DS: Direct Comparisons

To date, only a few studies have compared individuals with 22q-SZ to Schizophrenia patients with no known genetic deletion. An extensive literature search resulted in one study that compared these two groups on cognitive measures, and two studies that directly compared them on behavioral or symptom measures.

In a study of symptom characteristics, Murphy et al. (1999) screened 50 Caucasian patients with VCFS, and presumably 22q11DS, who were 17 or older. Of these, 15 (30%) had a history of psychosis, and 12 (24%) satisfied DSM-IV criteria for Schizophrenia. The VCFS Schizophrenia patients were then compared with a group of 12 non-22q-SZ patients who were matched on age, sex, marital status, and reproductive status. Using the Schedules for the Assessment of Positive (SAPS) and Negative Symptoms (SANS), these authors found no differences in positive symptoms between the groups, but they did find more severe negative symptoms in the non-22q-SZ group. Also, there were no differences between the two groups in global functioning, though patients in this study were more impaired (‘inability to function in almost all areas’) than those in the Bassett et al. (2003) study described below. In contrast, age of onset did differ between groups, with the 22q-SZ group showing a later age of onset (26 v. 19). Finally, they found that individuals with 22q11DS but not Schizophrenia had higher schizotypy scores than did normal controls.

In a subsequent study, Bassett et al. (2003) compared 16 adults with 22q-SZ with 46 adults with non-22q-SZ on a variety of symptom measures. Among these measures was the Positive and Negative Syndrome Scale (PANSS), which assesses the same domains as the SIPS. All of the 22q-SZ participants had IQs above 70 and were recruited from groups of psychiatric patients. The non-22q-SZ patients were all under age 50, had childhood–onset Schizophrenia, and were clinically stable.

These authors included six covariates in their analyses to account for differences between groups: sex, duration of illness, years of education, lifetime substance abuse, and two medication use variables. They found no group differences in age of illness onset (22.43 in non-22q-SZ and 20.81 in 22q-SZ), levels of current global functioning (in the range of 'some serious symptoms or impairment in functioning'), severity of positive or negative symptoms, anxiety-depression symptoms, or cognitive symptoms, as assessed by the Mini Mental Status Exam. However, the 22q-SZ group scored higher on 'poor impulse control,' 'uncooperativeness,' and 'hostility.' Further, 22q-SZ patients with mild mental retardation had higher positive and negative symptom scores than 22q-SZ patients without mental retardation.

To summarize, Murphy et al. (1999) found that 22q11DS patients with Schizophrenia had a later age at onset and less severe negative symptoms than non-22q11DS Schizophrenia patients. In contrast, Bassett et al. (2003) found no differences in age at onset or negative symptom severity, but did report more hostility and poorer impulse control. However, as noted by the authors, the 22q11DS sample in the Bassett et al. study was recruited through a psychiatric facility, and was therefore not originally diagnosed with 22q11DS based on physical signs. When patients with 22q-SZ are

recruited from psychiatric facilities, they would be expected to present as more similar to non-22q11DS Schizophrenia patients.

Study Goals and Hypotheses

In summary, both 22q11DS and SPD are associated with increased risk for the development of Schizophrenia and other psychoses (Asarnow, 2005; Shprintzen et al., 1992; Murphy et al., 1999; Gothelf et al., 2007; Pulver et al., 1994). Further, both groups manifest behavioral problems, as well as cognitive and structural brain abnormalities. With the increased emphasis on prevention of serious psychiatric disorders, researchers have intensified their focus on the identification of individuals at risk (McGorry et al., 2008). The ultimate objective is to develop standardized behavioral measures that will be capable of indexing 'profiles' that are sufficiently predictive of emergent psychosis to justify preventive intervention. Thus, further research on behavioral signs in at-risk populations has high priority.

The finding of a relation between the 22q11.2 deletion and psychotic disorders has been viewed as a landmark in the search for etiologic factors in major mental illness. It is possible that 22q-SZ represents a unique and specific etiologic subtype of Schizophrenia. Although research to date has not revealed any phenomenologic distinctions between 22q11DS and non-22q11DS Schizophrenia patients, it is possible that there are subtle differences. Moreover, these differences may be more apparent in the premorbid phase than they are after the clinical threshold for diagnosis is passed. Clearly, further research on the 22q11DS, especially in comparison to other risk groups,

holds promise for shedding light on the genetic mechanisms and developmental processes linked with psychosis.

To date, there have been no published studies that directly compare 22q11DS patients to those deemed at risk for psychosis based on clinical profiles (such as individuals with SPD). Yet, it is known that both groups are at heightened risk for onset of psychosis in young adulthood. Of particular interest are the behavioral profiles manifested by these two groups during the late adolescent/early adult period, as this is the developmental stage in which the functional decline leading to psychosis usually begins. Further, although researchers have made great progress in identifying the prodromal syndromes linked with risk for psychosis, there have been no investigations of prodromal symptoms or syndromes in 22q11DS. Thus, it is not known whether a subgroup of 22q11DS patients manifest a prodromal syndrome similar to that identified in retrospective and prospective studies of Schizophrenia. By better characterizing psychotic and prodromal syndromes in 22q11DS, opportunities for identifying the genetic determinants of psychotic symptom dimensions will be greatly improved.

The current study will address these issues by using standardized measures to examine both behavioral problems and prodromal symptoms in samples of 22q11DS and SPD youths. The following hypotheses will be tested:

Hypotheses

Hypothesis One

It is predicted that both the 22q11DS and SPD groups will manifest clinically elevated rates of behavior problems on the Child Behavior Checklist (CBCL; Achenbach

& Rescorla, 2001) when compared to healthy controls. It is also predicted that both groups will have more scores in the clinical range than the comparison group. Specifically, based on the CBCL findings in the Meyer et al. study (2005), it is predicted that the SPD group will show elevated scores on the anxious/depressed, withdrawn, somatic complaints, delinquency, social problems, and thought problems subscales, as well as on both broad factor scores (internalizing and externalizing problems) when compared to controls. Similarly, based on the overlapping findings in the 22q11DS CBCL literature (Heineman-de Boer et al., 1999; Lajiness-O'Neill et al., 2006; Nikklasson et al., 2005; Swillen et al., 1997; Feinstein et al., 2002; Debanne et al., 2006), it is predicted that the 22q11DS group will show elevated scores on the withdrawn, anxious/depressed, social problems, thought problems, and attention problems subscales, as well as on both factor scores. Further, given the high comorbidity with ADHD in both groups, as well as attenuated PPI and the implicated role of COMT in attention, it is predicted that both groups will show elevated attention problems scores. Because these two high risk groups have never been directly compared, there is no empirical basis for specific predictions regarding behavioral differences between the 22q11DS and SPD subjects.

Hypothesis Two

It is predicted that both the SPD and 22q11DS groups will show elevations on a standard measure of prodromal symptoms, the Structured Interview for Prodromal Symptoms (SIPS; McGlashan et al., 2003). More specifically, based on the diagnostic criteria for SPD and the aforementioned findings in 22q11DS of 'transient psychotic

episodes,' increased thought problems (Baker & Skuse, 2005; Bearden et al., 2004), and increased incidences of anxiety, mood, and autistic spectrum disorders, it is predicted that both groups will show elevated symptom scores in the positive, negative and disorganized symptom domains.

As described above, at least one previous study has shown that 22q11DS Schizophrenia patients have less pronounced negative symptoms than non-22q11DS Schizophrenia patients (Murphy et al., 1999). The present study will determine whether a similar difference in negative prodromal symptoms is observed when comparing the 22q11DS and SPD subjects.

Hypothesis Three

Given that both the 22q11DS and SPD groups are at heightened risk for psychosis, with estimates at or exceeding 25%, it is predicted that at least 25% of both groups will meet formal criteria for the SIPS "prodromal syndromes." Data on symptom duration were not used in the present investigation for two reasons. First, these data were not consistently available for individuals in the control and SPD groups. Second, while these duration criteria are clinically useful, the authors of the current investigation are aware of no published reports that demonstrate the discriminant or criterion validity of these duration criteria in prodromal diagnoses. In fact, conversion to psychosis has been associated with both stable individual characteristics/symptoms (Horan et al., 2008; Ekstrom et al., 2006), and changes during the prodromal period (Horan et al., 2008; Schultze-Lutter et al., 2007; Reichenberg & Goldenberg, 2006). Therefore, the presence of prodromal syndromes was investigated in the current study by assessing the number

and percentage of individuals that met symptom severity criteria for each of the three prodromal syndromes

Research Questions

In addition to testing the above hypotheses, the current study will shed light on several questions that have not yet been addressed in the literature. First, as previously mentioned, no study has yet compared individuals with SPD and 22q11DS on the CBCL, so it is not known whether these two groups differ on their behavioral problem profiles. Because the CBCL is so well validated and widely used in clinical assessment, it is an ideal measure for comparative studies of at-risk populations. Second, the current study will elucidate the nature of prodromal symptoms in the two risk groups. This is especially important with respect to 22q11DS, as it is not yet know whether these patients manifest the typical prodromal syndromes that have been observed in other at-risk populations. Patterns of convergence and divergence in symptom and behavioral profiles may have implications for theories positing the etiological overlap of these two groups

Method

Participants and Procedure

Participants for the present study are drawn from two ongoing longitudinal studies at Emory University; one focusing on SPD youth, and the other on youth with 22q11DS. In total, data were collected on 39 individuals with SPD, 51 controls, and 33 individuals with 22q11DS. Not all participants in the 22q11DS group had data for the

CBCL. Thus, ages differ slightly for the participants used in the investigation of the SIPS and CBCL.

Because the prodromal period is marked by a decline in function and a gradual increase in the severity of symptoms during adolescence/young adulthood, age becomes a very important variable. In investigating symptom differences between groups, it is important that the focus be on the same risk/susceptibility period in all participants. Thus, differences in CBCL and SIPS scores could potentially be confounded by age differences between diagnostic groups; if one group is older, it is possible that participants are, on average, further along in the prodromal period. Further, while age was only significantly correlated with scores on one of the CBCL subscales in the overall sample, a few significant correlations appear when parsing by diagnostic groups (Table 3). Further, age was positively correlated with a number of SIPS scales (negative, general, and disorganized symptoms), suggesting the need to account for confounding effects of age. Additionally, CBCL and SIPS scores are sensitive to behaviors that often differ in frequency at different age points. Thus, it becomes very important to account for age in any analysis involving the prodrome. While using age as a covariate allows for the inclusion of all participants, it also has the potential to obscure diagnostic group differences by partialing out age-related changes in symptoms (Adams et al., 1985; Miller & Chapman, 2001). Similar issues likely exist with gender and ethnicity, as well (table 3). Nonetheless, ANCOVA has the potential advantage of increasing power and sensitivity to detect interaction (Little et al., 2000). Therefore, in addition to conducting analyses using age, gender, and ethnicity as covariates, subjects were selected for a second set of analyses so that the three groups were optimally matched on these

demographics. Demographic characteristics of the overall sample are listed in table 1. Demographic characteristics of the samples in the age-matched analyses are listed in table 2.

22q11DS Adolescents

Details of the recruitment of 22q11DS participants are described elsewhere (Rockers et al., 2009*).* Briefly, participants were ascertained in reverse-age order from a case registry of individuals diagnosed with 22q11DS, which has been maintained at Children's Healthcare of Atlanta since 1996. Presence of the 22q11.2 deletion was confirmed in each case by Fluorescent In Situ Hybridization (FISH). These individuals were initially referred for FISH analysis either as children or adolescents, often due to the presence of heart defects, speech and language difficulties, and/or immunological problems. Individuals identified later in life were referred as part of clinical care within a Human Genetics Medical Clinic or Adult Heart Clinic.

After recruitment, patients underwent assessment at the Emory University 22q11DS clinic, a collaborative center maintained by researchers and physicians from Children's Healthcare of Atlanta and the departments of Human Genetics and Psychiatry and Behavioral Sciences at Emory University. This center is dedicated to both treatment and research. In total, data were collected from 33 individuals with 22q11DS, ranging in age from 14 to 29 at the time of their visits. SIPS data were collected for 23 22q11DS subjects and behavioral measures (CBCL/ABCL) were collected on all individuals. Ratings from the CBCL, which is designed for individuals aged 18 and younger, were available for 13 22q11DS subjects, while the other 20 had ABCL data. These two

instruments were designed to cover similar content areas and many of the same questions appear on both. Further, all but one of the factors is the same for both instruments. However, each instrument has many unique questions and the common factors/criterions differ based on age-appropriate behaviors. Further, during their development, factor analyses of individual items were done independently for the CBCL and ABCL in order to aggregate questions into factors (in fact, a few similar items load onto different factors on the two instruments). For these reasons, as well as the fact that only one of the three diagnostic groups has ABCL data, only CBCL data will be analyzed in the current study.

SPD adolescents

Individuals with SPD were recruited as part of the Emory University Adolescent Development Project. They were recruited through announcements seeking adolescents with diagnostic symptoms of SPD (stated in lay terms on recruitment materials). All potential participants were first screened over the phone to exclude those with possible Axis I diagnoses, mental retardation, or current substance abuse or addiction. Respondents deemed likely to meet criteria for SPD were invited to participate in the first, four-hour research assessment. Once in the lab, individuals were included in the SPD group on the basis of their SIDP-IV interviews, even if they also met criteria for other axis II disorder(s). In total, 39 participants met diagnostic criteria for SPD. These individuals ranged from age 11 to 18 at the time of their first visit. As part of a larger research protocol, they were administered the SIPS at every visit and their parents were asked to fill out the CBCL each time, as well. 23 of these adolescents were used in the matched SIPS analyses and 13 were used in the matched CBCL analyses (Table 2).

FISH analyses could not be performed on genetic data from the SPD group to check for the absence of the 22q11.2 deletion. Given Bayes' theorem, the aforementioned low base rates of the 22q11.2 deletion in Schizophrenia, and even lower rates in the general population, it is very unlikely that any individual in the SPD group would have the deletion. Nonetheless, the genetic data available were used to investigate this possibility. Specifically, 17 of the 39 SPD individuals had been genotyped for a previous project using two different markers in the COMT region on the 22q11.2 chromosomal region (RS4633 and RS4680). Of these 17, 9 (53%) were heterozygous at at least one of these markers, demonstrating the presence of two alleles at at least one locus on the 22q11.2 chromosomal region—precluding them from having a deletion. The other individuals were all homozygous at both loci, which does not rule out the possibility that they have a deletion.

Adolescent Controls

Individuals in the control group were recruited via two different routes. First, the majority were recruited through the Psychology Department registry for recruitment of healthy research participants. Potential participants were screened over the phone and selected for the control group because of the likely absence of any axis I or II diagnoses. Second, some individuals in the control group were originally invited to participate due to the possibility of their high risk status. These individuals were also screened over the phone, but were subsequently invited to participate based on the possibility that they would meet criteria for SPD or other high risk groups, but did not meet criteria for any

axis I or II diagnoses on any measure when they came in for their baseline assessment. Thus, the control group likely represents a broad range of normal behaviors.

In total, 51 individuals were placed in the control group; 30 of these controls are used in the demographic-matching analyses. These individuals ranged from age 11 to age 18 at the time of their first visit. 23 of these individuals were used in the matched SIPS analyses and 13 were used in the matched CBCL analyses (Table 2).

Just as in the SPD group, genetic data from the control participants could not be subjected to FISH analysis. Again, given the very low base rates of the 22q11.2 deletion in the general population, one would not expect to see it in the current control sample. To attempt to support the mutual exclusivity of the diagnostic groups, the two COMT markers were again checked. Of the 30 control individuals used in these analyses, 20 had been genotyped. Of these, 10 (50%) were heterozygous at at least one of the two loci. The remainder of the controls were homozygous at both loci.

Measures

Structured Interview for DSM-IV Personality (SIDP-IV)

The SIDP-IV (Pfohl et al., 1997) is a semi-structured interview used to assess for the presence of DSM-IV Axis II disorders. It asks a number of questions about interests and behaviors, work styles, relationships, emotions, perceptions of self and others, stress and anger, and social conformity, each of which maps onto DSM-IV Axis II diagnostic criteria. The interviewer scores each question on a discrete 0-3 scale; these numbers represent not present, subthreshold, present, and strongly present, respectively.

Subsequently, scores of present and strongly present are used to assess the presence of Axis II symptoms and diagnoses.

The SIDP-IV was only administered to individuals in the control and SPD groups. Those with the 22q11.2 deletion were included in the 22q11DS group, regardless of diagnostic status.

Structured Interview for Prodromal Syndromes (SIPS)

The SIPS (McGlashan et al., 2001) is a semi-structured diagnostic interview designed to assess and diagnose the severity of Prodromal symptoms of Schizophrenia. It is composed of 19 symptom-items, each rated on a 0-6 scale. Scores of 0 indicate the absence of a symptom while scores of 1-2 indicate the non-prodromal presence of a symptom. Scores between 3 and 5 are considered to be within the prodromal range and a score of 6 is in the psychotic range. Each item is comprised of a number of questions that allow the interviewer to accurately rate the severity of each symptom. The 19 symptom-items are grouped into four symptom scales: positive, negative, disorganized, and general symptoms.

The positive symptom scale consists of items that assess unusual thought content and delusional ideas, suspiciousness and persecutory ideas, grandiosity, perceptual abnormalities and hallucinations, and disorganized communication. The negative symptom scale includes items that assess social anhedonia, avolition, reduced expression of emotion, decreased experience of emotion and self, ideational richness, and deterioration of role functioning. Items on the disorganized symptom scale assess odd behavior or appearance, bizarre thinking, trouble with focus and attention, and

impairment in personal hygiene. Finally, the general symptom scale contains items that assess sleep disturbance, dysphoric mood, motor disturbances, and impaired tolerance to stress. Each symptom scale also yields a factor score, comprised of the average of all the items within that scale.

Scores on these symptom dimensions are used to determine whether subjects meet criteria for one or more prodromal syndromes; namely, the attenuated positive syndrome (APS), or the brief intermittent psychotic syndrome (BIPS). The APS is characterized by the presence of at least one subthreshold positive symptom and no psychotic level positive symptoms. In BIPS, an individual experiences at least one psychotic level positive symptom which must have developed or increased to psychotic intensity within the past three months. In addition to these prodromal syndromes, the SIPS can also classify individuals as meeting criteria for Presence of Psychotic Syndrome (POPS). Criteria for POPS are similar to those of APS except that individuals have at least one positive symptoms rated as 'psychotic.' All participants in the current study were administered the SIPS at each assessment period.

Achenbach System of Empirically Based Assessment; Child Behavior Checklist (CBCL)

The CBCL is a behavioral rating scale designed to assess "diverse aspects of adaptive and maladaptive functioning (Achenbach & Rescorla, 2001)." It is completed by parents or others who see an individual between the ages of 6 and 18 in a home-like setting and is comprised of 113 items scored from 0 to 2. A score of 0 represents an answer of 'not true,' 1 represents 'somewhat or sometimes true,' and a score of 2 represents an answer of 'very true or often true.' Items cluster into 9 factors:

anxious/depressed, withdrawn, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior (delinquency), and aggressive behavior. Two additional factors, internalizing and externalizing problems, are also available. A third, total problems factor, is also available but is not analyzed in the current study. Because a fourth 'other problems' factor is comprised of items that didn't cluster into a unitary factor, it is also not analyzed in the current study. Parents of participants in all three groups in the current study completed the CBCL before each visit or follow-up.

Results

SIPS

Diagnostic Group Comparison of SIPS Ratings: Demographic-Matched Groups.

To test for diagnostic group differences in SIPS subscale ratings, a MANOVA was performed using diagnostic status (SPD, 22q11DS, and normal controls) as the between subjects factor and the 4 SIPS global symptom scores as the within-subjects factors. These analyses were conducted on the age, gender, and ethnicity-matched samples, which included 23 participants in each diagnostic group. The demographic breakdown of these participants is summarized in table 2 and correlations between demographic data (age, gender, and ethnicity) and SIPS outcome scores are listed in table 3.

Box's Test of covariance homogeneity was significant for the omnibus MANOVA ($F(20, 15636.113) = 3.106$, $p<.001$), suggesting that the assumption of equal variance/covariances across dependant variables between groups had been violated. However, Leech and colleagues (2004) suggest that MANOVA is robust to this violation

if sample sizes within groups are equal. They suggest that Pillai's trace statistic be used in this case. Given that all three groups in the present analysis have identical sample sizes, Levene's tests were conducted on each of the symptom variables to test for homogeneity of variance. Results showed that variances differ between groups on all four of the symptom scales (positive symptoms: $F=12.138$, $p<.001$; negative symptoms: $F=5.502$, $p=.006$; disorganized symptoms: $F=7.025$, $p=.002$; general symptoms: $F=8.609$, $p<.001$). Raw group means are illustrated in Figure 1 and all SIPS scores are listed in Appendix 1.

Skewness statistics for these SIPS data are shown in Appendix 2. Given the observed heterogeneity of variance, partially due to floor effects in the normal control group and positive skew across all groups, data transformations were indicated. However, comparisons between the two clinical groups in their original metrics are of central importance in the current study because these metrics are used to qualify individuals as prodromal or psychotic. Therefore, the possibility of keeping SIPS data in their raw form for comparisons between the SPD and 22q11DS groups was investigated by conducting analyses without the control group. Unfortunately, Levene's tests performed separately on each SIPS item indicated that on 22q11DS and SPD data, variances differed for positive symptoms: $F(1,44) = 16.340$, $p = .0002$; negative symptoms: $F(1,44) = 4.587$, $p = .0378$; and general symptoms: $F(1,44) = 4.658$, $p = .0364$). Thus, data transformations were performed on all SIPS data. These were seen as preferable to non-parametric tests because the latter are less powerful at detecting group differences and group n's in the present study are relatively small.

Again, visual inspection of SIPS data, as well as positive skewness values for all combined groups (appendix 2) indicated the presence of positive skew in all the SIPS variables. Neither a square root transformation (Keppel & Wickens, 2004) nor a logarithmic transformation successfully equalized the majority of variances. Therefore, the Games-Howell contrast procedure was used to investigate group differences within each dependant variable in lieu of using MANOVAs. Briefly, Games-Howell is a modification of the Tukey test, and therefore indicated when all possible comparisons are being run. It was seen as better than Tamhame's T2 for these data because it is slightly more conservative and the current analysis involves a large number of comparisons. Unfortunately, this procedure does not correct for distributional deviations from normality. Thus, results should be interpreted with caution.

As predicted, both the SPD and 22q11DS groups had higher scores than controls using Games-Howell contrasts on the positive symptom factor ($p < .0001$ and $p = .0001$, respectively), the negative symptom factor ($p = .0014$ and $p < .0001$, respectively), and the disorganized factor ($p < .0001$ for both), as well as on the general symptoms factor ($p = .0001$ and $p<.0001$, respectively).

Finally, figure 1 suggests similar profiles of SIPS scores for the clinical groups in the overall factor scores. To further explore diagnostic group differences in symptom profiles, a repeated measures ANOVA was conducted to determine whether non-parallel patterns were evident as a group X symptom scale interaction. The model displayed heterogeneous group covariances (Box's M: $F(10, 9255.777) = 2.036$, $p = .026$), but did not violate the assumption of sphericity (Mauchly's $W = .847$; $\chi^2(5) = 7.1$; $p = .213$).

While the interaction term in this model neared significance ($F(3,132) = 2.223$, $p = .088$), it did not reach the alpha = .05 threshold.

Diagnostic Group Comparison of SIPS Ratings: Demographic-Controlled Analyses.

Kruskall Wallis Chi Square analyses revealed that, in the overall sample, diagnostic groups differed with respect to age ($\chi(2) = 13.524$, $p = .001$), but not ethnicity ($\chi^2(2) = 4.433$, $p = .109$) or gender ($\chi^2(2) = 2.917$, $p = .233$). However, correlations between gender and SIPS factor scores as well as between ethnicity and SIPS factor scores suggest that the relationship between these covariates and SIPS scores differ by diagnostic group (table 3). Thus, a set of analyses was run using a regression framework to control for the effects of these covariates, partialing out the variance in dependent variables associated with variability in these covariates. Subsequently, orthogonal ANCOVA contrasts were computed, comparing the control group to the combined clinical groups and comparing each clinical group to the other. These analyses were conducted using no covariates, each covariate independently, and all covariates together to further investigate the influence of these covariates. Additionally, these models were run twice: first with all subjects for whom SIPS data were available, and second excluding 8 individuals from the 22q11DS group who were older than any participants in either of the other two groups.

Results of the SIPS covariance analyses are summarized in Tables 4 and 5. Table 4 includes R^2 values for both contrasts together, as well as the significance of each contrast when looking at the whole model. Table 5 includes R^2 values and significance of contrasts as they were entered into the model. Briefly, age accounted for a significant

amount of variance in SIPS scores in the negative, disorganized, and general symptoms models, but only when the larger subject group was used. This was true both when all three covariates were included and when only age was included. Ethnicity was a significant covariate for all SIPS factor scores when entered without other covariates in the smaller subject group. It was also significant for the disorganized symptoms model in the larger group. When entered alone, gender was a significant covariate for the positive, negative, and disorganized symptom models in both subject groups and was significant for all models when all three covariates were included in the models.

Diagnostic group contrasts between controls and the combined clinical groups were significant at the $p<.001$ level in all models for all four SIPS factors; clinical groups had higher scores than the control groups. R^2 values for these contrasts are listed in table 5 and varied around .3. Thus, they were roughly moderate in size and accounted for around 30% of the variance seen in SIPS scores. Contrasts between the 22q11DS and SPD groups were significant for the positive symptoms factor in both sets of models with all combinations of covariates (R^2 values ranged from .288 to .33), with the SPD group demonstrating higher scores. Additionally, the 22q11DS v. SPD contrast was significant for the negative symptoms factor in the larger group when using only gender as a covariate ($R^2 = .326$, $p = .031$) and marginally significant when using all covariates ($R^2 = .281$, $p = .054$), with the 22q11DS group showing higher scores. However, this contrast was only significant when variance in negative symptoms associated with the clinical v. non-clinical contrast was accounted for. SPD and 22q11DS individuals did not significantly differ in any model for the SIPS general or disorganized symptom factors.

Finally, a set of analyses was run to determine the level of power associated with these diagnostic group contrasts. When power was inadequate for detecting significant results given the observed effect sizes, the number of participants required for power of 80% was computed. These results are listed in table 5. Briefly, where effect sizes were moderate or larger, the current study was adequately powered to yield significant findings. However, when effect sizes were small or small-to-moderate in size, the current study was underpowered (with power less than 80%); the sample sizes in the current study were inadequate to detect significant effects that were small in size.

SIPS: Summary

In summary, results of the SIPS covariance analyses were similar to those of the covariate-matching analyses. In both the analyses matching and controlling for demographic factors, 22q11DS and SPD groups had higher scores than controls on the SIPS positive, negative, disorganized, and general symptom factor scores. These contrasts typically accounted for roughly 30% of the variability in SIPS scores. When matching for demographic variables, the two clinical groups did not differ from each other on any SIPS factor score. However, when covarying for demographic variables, the SPD group did show significantly higher positive symptom scores than the 22q11DS group, while their negative symptom scores were lower than the 22q11DS group with trend-level significance. These contrasts accounted for 6.7 and .2% of the overall variance in SIPS scores, respectively, though their influence increased once variance due to the clinical v. non-clinical groups was partialed out (with significant correlation coefficients of .266 and -.235 for the positive and negative symptoms contrasts,

respectively). The combined clinical groups showed significantly higher scores than the controls on the general symptom scale in only the covarying analyses.

Controls had average factor scores in the 'not present' to 'questionably present' range, while both high-risk groups had scores in the 'questionably present' to 'mild' range. Additionally, there was no group X symptom scale interaction between the two high-risk groups, though results were marginally significant, possibly due to non-significantly higher positive symptom scores in the SPD group and non-significantly higher negative symptom scores in the 22q11DS group. Additionally, power analyses on the models covarying for demographic differences revealed that the current study is underpowered to detect diagnostic group differences that are small in size. Finally, age, gender, and to a lesser extent, ethnicity, appear to be important factors in SIPS scores.

CBCL

Diagnostic Group Comparison of CBCL Scores: Demographic-Matched Groups.

Group means for all CBCL subscales can be seen in table 6 and illustrated in figure 2. To investigate differences between groups across the CBCL subscales, two MANOVAs were performed with the demographic-matched data, again using diagnostic status as the between subjects factor and CBCL subscale scores, then CBCL factors scores as the dependant, within subjects factors. Correlations between demographic variables and CBCL outcome scores are summarized in Table 3. In the first MANOVA, using only the subscale scores, Box's test of equality of covariances ($F(72,3611.075) = 1.988$; $p<.0001$) was significant, suggesting that the assumption of equal variance/covariances across dependant variables between groups has been violated.

However, given that all three groups have n's of 13, the omnibus MANOVA ($F(16,60) = 2.703$, $p=.003$) can be interpreted and is significant. Levene's tests indicated that the assumption of homogeneity of variance for between subject factors was not violated for the anxious/depressed, withdrawn, social problems, thought problems, attention problems, delinquency, or aggression subscales (all p's above .19), but was violated for the somatic complaints ($F(2,36) =4.623$; $p=.016$) subscale. For comparison purposes the authors elected to keep this subscale in its raw form and simply interpret results with caution.

In the second MANOVA, using the internalizing and externalizing factor scores as dependant variables, Box's test was significant (Box's $M = 15.528$, $F(6,32300.308) = 2.38$, $p =.027$), though neither Levene's test was significant ($F(2,36) = 2.205$, $p = .125$ and $F(2,36) = .688$, $p = .509$ for internalizing and externalizing scores, respectively). The omnibus ANOVA was significant ($F(4,72) = 7.309$, $p<.001$).

Results of the between subjects effects were significant at $p = .05$ for all subscales except somatic complaints ($F(2,36) = 1.678$, $p =.201$) and delinquency ($F(2,36) = 2.887$, $p = .069$): (anxious depressed: $F(2,36) = 15.077$, $p < .0001$; withdrawn depressed: $F(2,36) = 4.436$, $p = .019$; social problems: $F(2,36) = 15.097$, $p < .0001$; thought problems: $F(2,36) = 7.177$, $p = .002$; attention problems: $F(2,36) = 7.879$, $p = .001$; aggression: $F(2,36) = 3.636$, $p = .036$). They were also significant for both factors (internalizing problems: $F(2,36) = 13.031$, $p < .0001$; externalizing problems: $F(2,36) = 5.177$, $p = .011$). These results are summarized in Table 6 and illustrated in Figure 2

Before performing post-hoc comparisons, planned comparisons (comparing the clinical groups to the control group) were conducted on all subtests for which there were

a priori directional hypotheses. For all comparisons, an alpha of .01 was used to reduce the likelihood of Type I errors associated with performing multiple comparisons. Group means can be found in table 6, where significant contrasts are also denoted.

Planned comparisons contrasting the SPD and control groups indicated that the SPD group had significantly higher scores on the anxious/depressed ($t(36) = 5.345$, $p<.0001$), withdrawn ($t(36) = 2.945$, $p=.005$), social problems ($t(36) =5.457$, $p<.0001$), thought problems ($t(36) =3.704$, $p=.0007$), and attention problems ($t(36) =3.903$, $p=.0004$) subscales, as well as the internalizing ($t(36) = 5.076$, $p<.0001$) factor score. The comparison was marginally significant for the externalizing factor ($t(36) = 2.696$, $p=.011$), with the SPD group again showing higher scores. Because the between-subject F was not significant for the somatic complaints or delinquency scales, these were not investigated.

Planned comparisons contrasting the 22q11DS group and the control group also indicated that the 22q11DS group had significantly higher scores on the social problems ($t(36) = 3.284$, $p=.0023$) subscale, and the internalizing ($t(36) = 3.007$, $p=.0048$) factor score. The difference was not significant for the anxious/depressed ($t(36) = 1.581$, $p=.1227$), withdrawn ($t(36) = 1.856$, $p=.0716$), thought problems ($t(36) = 1.163$, $p=.2525$), and attention problems ($t(36) = 1.326$, $p=.1931$) subscales, or for the externalizing ($t(36) = .173$, $p=.8637$) factor score.

To address the aforementioned exploratory research questions, post-hoc tests were performed on all other comparisons, with two tailed p-values adjusted using the Bonferroni correction to account for multiple comparisons. Significant differences are denoted in table 6. Specifically, the SPD group had significantly higher scores than the

22q11DS group on the anxious/depressed subscale (p=.002) and on the externalizing problems factor (p=.021). Differences were marginally significant on the thought problems (p=.046) and attention problems (p=.043) subscales. The SPD group did not differ from the control group on the aggression subscale (p=.095). The 22q11DS group only differed from the control group on the internalizing (p=.014) factor.

As illustrated in Figure 2, on average, the control and 22q11DS groups were below the clinical t-score cut off of 65 on all CBCL subscores. In contrast, the SPD group was above the clinical cutoff for the anxious/depressed (M = 73.62, SD = 11.594), withdrawn (M = 68, SD = 10.288), social problems (M = 10.08, SD = 9.340), thought problems (M = 70.62, SD = 11.207), and attention problems (M = 67.54, SD = 9.863) subscales, as well as the internalizing (M = 70.85, SD = 9.814) factor (but not the somatic complaints, delinquency, aggression, or externalizing subscales).

Finally, in Figure 2, it appears as if the relative pattern of peaks and valleys for the two clinical groups is parallel, suggesting that despite a baseline difference, the two groups show similar patterns of CBCL scores. Consistent with this, repeated measures ANOVAs yielded non-significant interaction effects (all subscales except anxious/ depressed subscales: $F(3.771,90.5) = .559$, $p = .683$; factor scores: $F(1.115,26.767) = .672$, $p = .435$).

Diagnostic Group Comparison of CBCL Scores: Demographic-Controlled Analyses

Kruskall Wallis Chi Square analyses revealed that, in the overall sample, diagnostic groups did not differ with respect to age ($\chi(2) = .772$, $p = .680$), ethnicity ($\chi^2(2) = 4.287$, $p = .117$), or gender ($\chi^2(2) = .779$, $p = .677$). However, just as on the

SIPS, correlations between demographic variables and CBCL item scores suggest that the relationship between these covariates and SIPS scores differ by diagnostic group. These correlations are listed in table 3. Thus, a set of analyses were again run using a regression framework to partial out the effects of these covariates. Subsequently, orthogonal ANCOVA contrasts were computed, again comparing the control group to the combined clinical groups, then comparing each clinical group to the other. These analyses were conducted using no covariates, each covariate independently, and all covariates together.

Results of the covariate-controlled analyses are summarized in tables 7 and 8. Briefly, gender was never a significant covariate for either contrast, regardless of whether it was entered by itself or along with other covariates. Similarly, age was only a significant covariate for the thought problems subscale, but it was significant both when entered alone and when included along with the other two covariates. Ethnicity, however, accounted for a significant amount of variance in all but the thought problems and delinquency subscales when included as the only covariate in the model, and all except thought problems, delinquency, and aggression when all covariates were included.

Table 8 shows R^2 and p values for all diagnostic contrasts for all covariate models. To summarize, when partialing out the variance in CBCL scores associated with all three covariates, the combined clinical groups (control n = 51, SPD n = 39, 22q11DS n = 14) had significantly higher scores than controls on the anxious/depressed (R^2 = .07, p = .001), withdrawn (R^2 = .087, p = .001), social problems (R^2 = .091, p <.001), and thought problems subscales (R^2 = .08, p = .002), as well as on the internalizing factor (R^2 = .111, p <.001). These contrasts accounted for around 10% of the variance in these

CBCL scale scores. When comparing the two clinical groups, the SPD group had significantly higher CBCL scores than the 22q11DS group on the anxious/depressed (R^2 = .173, p >.001), social problems (R^2 = .101, p = .001), thought problems (R^2 = .104, p = .001), attention problems (R^2 = .089, p = .002), delinquency (R^2 = .06, p = .012), and aggression subscales (R^2 = .065, p = .009), as well as on the externalizing factor (R^2 = .077, p = .004). Last, CBCL results were subjected to power analyses, which are summarized in table 8. In both sets of contrasts, power was again adequate when effect sizes were moderate or larger, but inadequate to detect effects that were smaller in size.

CBCL Summary

In summary, when matching for age, gender, and ethnicity, both high risk groups showed higher scores than controls on the social problems item and internalizing factor on the CBCL. In both, the SPD group was in the clinically elevated range while the 22q11DS group was slightly below the clinically significant cutoff. In addition, only the SPD group differed from controls on the anxious/depressed, withdrawn, thought problems, and attention problems scales, as well as on the externalizing factor. All of these except the externalizing factor were in the clinically significant range for the SPD group, though none of the elevations in the 22q11DS group were in the clinically significant range.

Comparing the SPD and 22q11DS groups to each other in the matching analysis, the two groups only differed from each other on the anxious/depressed, thought problems, and attention problems items, as well as on the externalizing problems factor. In each of these high-risk group differences, the SPD group had higher scores, which

were in the clinically significant range for all scales. However, when including all participants and partialing out variance in CBCL scores due to these demographic factors, the SPD group also had significantly higher social problems, delinquency, and aggression scores than the 22q11DS group.

In the CBCL covariance analyses, ethnicity was a significant covariate in multiple models, while gender was never significant. Age only played an important role on the thought problems scale. Finally, power analyses again suggested that the current study is not adequately powered to detect significant effects that are small in size.

Prodromal Syndromes

To explore the final hypothesis, the presence of two different prodromal syndromes was investigated in the current study's participants—Brief Intermittent Psychotic Symptom Syndrome (BIPS) and Attenuated Positive Symptom Syndrome (APS). Each of these syndromes is based on criteria that address SIPS symptom severity. The designation of APS corresponds to a rating at the severity level of 3 ("moderate") to 5 ("severe") on any positive symptom, with ratings of 6 considered in the psychotic range.

Results are summarized in Figure 3. 10 controls (19.608%), 24 participants with SPD (61.538%), and 19 22q11DS individuals (55.882%) met symptom criteria for APS and 1 22q11DS individual (2.941%) met BIPS criteria. Thus, in total 19.608% of the control sample, 61.538% of the SPD sample, and 58.823% of the 22q11DS sample met symptom criteria for a prodromal syndrome. Additionally, 4 SPD individuals (10.256%) and 1 22q11DS individual (2.941%) met POPS criteria. Kruskal-Wallis Chi-Square tests

revealed that rates of APS differed between diagnostic groups ($\chi 2(2) = 20.790$, p =< .0001), rates of BIPS ($\chi^2(2) = 2.903$, p = .234) did not, but rates of overall prodromal syndromes did differ ($\chi^2(2) = 22.21$, p<.001. POPS rates also differed between groups (χ^2**(2)** = 5.906, p = .052).

Discussion

The present study examined behavioral problems and symptoms in two groups of adolescents known to be at risk for psychosis. As expected, when compared to age-, gender-, and ethnicity-matched controls, both of these groups manifested significantly more behavioral problems and greater severity of prodromal symptoms. Further, these elevations resulted in behavioral and symptom profiles that are phenomenologically similar. Nonetheless, there were also some differences between the two risk groups. The SPD group generally manifested more severe behavior problems and symptoms than the 22q11DS group, though there were some notable exceptions to this. In particular, while the 22q11DS group showed behavioral problems intermediate in severity to those of the control and SPD groups, they showed no elevated externalizing problems (including aggression and delinquency), while the SPD group did, and fewer social problems. There also appear to be differences in the severity of positive and negative symptoms between the two high-risk groups. In the following sections, the nature of the group differences, and their implications, are discussed.

Diagnostic group differences in behavior problems (CBCL)

SPD v. Control groups

As predicted, the SPD group had significantly higher scores than the control group on the anxious/depressed, social problems, thought problems, and attention problems scales, as well as on the internalizing and externalizing factors. These findings generally replicate a previous report by Meyer, et al. (2005), which showed that SPD youth had elevated scores on the CBCL anxious/depressed, somatic complaints, delinquency, social problems, attention problems, and thought problems subscale scores, as well as on the two broad factor scores. Further, all of these scales, except for the externalizing factor score, were in the clinically significant range for the SPD group. Finally, in addition to these hypothesized elevations, the SPD group was found to have higher scores than the control group on the withdrawn factor, which is consistent with diagnostic criteria for that condition.

The SPD group did not show clinically or significantly elevated somatic problems or delinquency scores in the demographic-matching analyses, as had been predicted. However, the SPD group did score non-significantly higher than the control group on these scales, with moderate-to-large effect sizes (somatic complaints: Cohen's d = .655; delinquency: Cohen's d = .740), suggesting that small sample sizes reduced power for detecting these differences. In fact, these scores were significantly higher than controls in the combined clinical group on the somatic complaints scale in the covariance analyses. These findings both corroborate those of the Meyer, et al. study and lend support to the notion that SPD is associated with a range of parent-rated behavioral problems.

Of course, heightened parent-reported behavior problems are to be expected in the SPD group, given that the subjects were recruited based on the presence of behavioral problems. However, the present findings shed light on the scope and severity of these behaviors. In general, the psychosis prodrome and SPD entail subthreshold 'core' symptoms of Schizophrenia. The current results suggest that individuals with SPD also show elevated behavioral problems on a standard scale designed to measure problem behaviors in clinically referred children. The CBCL scale elevations manifested by the SPD group roughly correspond to the three symptom dimensions that characterize the prodrome; positive symptoms (thought problems, externalizing problems), negative symptoms (attention problems, social problems, internalizing problems), and affective symptoms (anxious/depressed, withdrawn).

22q11DS v. Control

Like the SPD subjects, the 22q11DS patients manifested CBCL scale elevations, though these were less pronounced in severity. Based on previous reports, it was hypothesized that the 22q11DS group would show elevated scores on the withdrawn, anxious/depressed, social problems, thought problems, and attention problems scores, as well as on both broad factors. These predictions were partially supported.

As predicted, the 22q11DS group showed more behavior problems than the control group. However, the breadth and magnitude of the difference was not as large as predicted: The 22q11DS group had higher scores than the control group on the social problems scale and the internalizing problems factor in the demographics-matched analyses. While none of the subscale or factor scores were in the clinically significant

range, the withdrawn and social problems scales neared the threshold of t = 65 (and were above the threshold of t = 60 used in the study by Heineman-de Boer and colleagues (1999)). These results suggest that this sample of individuals with 22q11DS show internalizing behavior problems characterized by social difficulties and internalized mood symptoms, but, unlike the SPD group, no significant externalizing problems.

This pattern of findings for the 22q11DS group is consistent with a number of previous investigations that also showed elevated internalizing factor scores (Heineman de Boer et al., 1999) and social problem scores (Lajiness-O'Neill et al.,2006; Swillen et al., 1997; Feinstein et al., 2002). Further, the present findings of increased internalizing and social problems in 22q11DS accord well with the clinical picture generally used to describe these youths. However, one of the most consistent findings in the previously discussed literature on the CBCL in 22q11DS was elevated attention problems scores (Nikklasson et al., 2005; Swillen et al., 1997). The current study did not demonstrate clinically or significantly elevated attention problems in 22q11DS.

Figure 1 indicates that, with the exception of externalizing problems (including delinquency and aggression), the 22q11DS group shows elevations in all CBCL scores over those of the control group (with moderate Cohen's d effect sizes ranging between .506 and .751 for the non-significant contrasts). Again, the small sample sizes, combined with a strenuous alpha criterion for post-hoc comparisons reduced statistical power. Power analyses conducted on diagnostic group contrasts in the larger covariance analyses revealed that the current study is underpowered at detecting true effects that are small in magnitude (with sample sizes in the hundreds required to detect these effects). Given that the age matching analyses used smaller sample sizes, it is likely that further

investigation with higher powered studies would find these differences to be statistically significant.

SPD v. 22q11DS

The primary focus of the current study was to compare the prodromal symptomatology of 22q11DS and SPD. As mentioned, there are no previous studies in which these two groups have been directly compared. Although there was no theoretical and little empirical basis for predictions, some previous reports suggested that the SPD group would show higher scores than the 22q11DS group on the somatic complaints and delinquency subscales. This hypothesis was not supported for either subscale in the demographic-matching analyses: neither group scored in the clinically significant range nor differed from controls on either subscale. However, in more than one of the demographic-covaried models, the SPD group showed significantly higher scores than the 22q11DS group on both subscales. Further, a large effect size for the contrast between SPD and control patients on the delinquency subscale (Cohen's d = .837) suggests that the SPD group may again show significantly elevated scores in higher powered studies (19 subjects in each group would be required to achieve power of 80%). The same may hold for somatic complaints for both clinical groups (SPD v. controls: Cohen's d=3.000; 22q11DS v. controls: Cohen's d=.506), though one would have expected the 22q11DS group to have the highest scores given the myriad physical problems that typically plague these individuals. Additionally, it is noteworthy that in the 22q11DS group, the delinquency (Cohen's d = .111), aggression (Cohen's d = .070), and overall externalizing problems (Cohen's d = .062) scores were nearly the same as those

for controls. This suggests that externalizing behaviors are not part of the clinical picture in 22q11DS, but are in SPD.

There were also significant differences between the 22q11DS and SPD groups on several of the other CBCL scales. Specifically, in both types of analyses, the SPD group had higher anxious/depressed, thought problems, and attention problems subscale scores, as well as higher externalizing factor scale scores, than the 22q11DS group. Additionally, the SPD group showed higher scores than the 22q11DS group on the social problems and aggression problems in the covariance analyses.

Given that individuals in the SPD group were selected for participation based on the presence of subthreshold positive symptoms, it is not surprising that they manifest higher CBCL thought problems scores than both of the other diagnostic groups. Nonetheless, based on evidence that the eventual rate of psychosis in the two risk groups is comparable, the present findings suggest that the predictive power of subclinical thought disorder may differ between the two groups. Further, age emerged as a significant covariate on only the thought problems scale. Thus, it is possible that these differences in predictive power may be affected by small differences in age or other developmentally-related factors that differ among participants.

Depressed mood is often considered part of the clinical picture in SPD, possibly explaining the current finding of increased anxious/depressed scores in that group. However, rates of clinically diagnosable mood disorders in 22q11DS have been assessed as being as high as 52% in previous studies (Popolos et al., 1996). Thus, it is also possible that the sample used in the current study shows uncharacteristically low rates of mood problems. Similarly, the finding of more attention problems in the SPD group is

somewhat discrepant with the high rate of comorbid ADHD diagnoses typically found in 22q11DS (Niklasson et al., 2005; Baker & Skuse, 2005; Popolos et al., 1996;). It is possible that non-attentional illness-related phenomena make individuals with SPD appear inattentive to the parents who complete their CBCL ratings. It is also possible that the procedures used to recruit participants with the 22q11.2 deletion in the current study resulted in participants with less severe pathology—many studies of 22q11DS use participants recruited from clinical, rather than medical settings. If this is the case, however, it is likely that the current sample is more representative of the deletion syndrome, as it occurs in the general population.—making phenotypic similarities more relevant.

Regardless, with the exception of the differences in externalizing behaviors, the 22q11DS and SPD groups show relatively parallel patterns of CBCL scores (see Figure 2), with the scores of the 22q11DS group intermediate to those of the control and SPD groups. This pattern was confirmed by the absence of a group X subscale interaction, suggesting a qualitative overlap in the behavioral profiles of these two groups, with SPD showing a relatively consistent baseline elevation when compared to the 22q11DS group. In other words, with the exception of externalizing problems, both groups show either significant or trend-level elevations on the same CBCL subscales, with the SPD group showing somewhat more severe deficits. These findings are consistent with the notion that vulnerability to psychosis in both risk groups results from similar mechanisms, possibly stemming in part from genes on the 22q11.2 chromosomal region (Gottesman & Gould, 2003). They also suggest that the behavioral phenotype seen in SPD is a more severe form of that seen in 22q11DS, with the addition of increased externalizing

problems. At present, of course, it is not possible to rule out equifinality—in other words, that SPD and 22q11DS represent divergent pathways that lead to similar behavioral phenotypes.

Finally, investigating the role of age, gender, and ethnicity as covariates in the regression/ANCOVA analyses revealed that differences in ethnicity, though not gender or age (outside of the thought problems scale), explains a significant amount of variance in CBCL scores. Age was likely not significant because the current study used only CBCL parent report forms, which restrict the ages of individuals to 18 years or under. Thus, it is possible that age would have played a larger role had a less restricted range been assessed. Nonetheless, this result suggests that ethnicity may be an important variable to account for when assessing behavior problems in youths at risk for psychosis—different ethnic/cultural groups may differ in what they see as representing 'problematic behaviors.'

Diagnostic group differences in prodromal symptoms (SIPS)

The second hypothesis, that both clinical groups would show elevated prodromal symptom scores, was also partially supported. Both groups showed higher scores than controls on all four of the SIPS symptom domains in both sets of analyses. While no a priori hypotheses about how the two clinical groups would differ could be made, these two groups are contrasted below:

Clinical v. Control Groups

In the SPD group, it was predicted that SIPS scores would be elevated on the positive, negative, and disorganized symptom scales. Results supported these hypotheses; the SPD group had average domain scores higher than controls on the overall positive, negative, and disorganized factors. These scores had averages in the 1-2 range, qualifying them as 'questionably present' to 'mild.' The SPD group also had significantly higher general symptoms scale scores than controls, also in the 'questionably present' to 'mild' range. Thus, as would be expected based on the DSM-IV criteria for SPD, the SPD group showed subthreshold positive ('psychotic' and 'disorganized'), negative, and affective symptoms of Schizophrenia, relative to controls. Further, as would be expected based on evidence that only a subgroup of youth with SPD go on to develop axis I psychotic disorders, the mean scores on the SIPS symptom ratings were generally in the subthreshold level. Thus, the SPD group contains a subgroup that would be classified as meeting SIPS criteria for the prodrome. Scores for individual SIPS items are listed in appendix 1. While individual scores are generally seen as unreliable, the finding that all but one of the scale and subscale scores (sleep disturbance) in controls were in the 'not present' to 'questionably present' range is consistent with the notion that far fewer of these subjects are at risk for psychosis.

Consistent with predictions, when compared to the control group, the 22q11DS group also had higher scores on the positive ('questionably present' to 'mild' range), negative (average around the 'mild' range), and disorganized (average scores in the 'questionably present' to 'mild' range) symptom scale scores. They also had higher scores on the general symptoms scale, where the average was again in the 'questionably

present' to 'mild' range. As in the SPD group, this pattern of results suggests that individuals in the 22q11DS group also showed subthreshold positive, negative, and affective symptoms of Schizophrenia. This profile supports the study of the psychosis prodrome in 22q11DS patients.

SPD v. 22q11DS

As illustrated by Figure 1, the profiles of SIPS symptom scale scores is similar for the SPD and 22q11DS groups. In the demographic-matching analyses, there is a trend toward more positive symptoms for the SPD group that achieves significance in the covariance analyses. This is consistent with the pattern of scores seen on the CBCL, where the 22q11DS group showed lower thought problems scores than the SPD group, and scores intermediate to those of the SPD and control groups on all scales except the externalizing subscales and factor. Perhaps more remarkable is the fact that positive symptom scores are not more discrepant between the two groups, given that the SPD group was selected for the presence of prodromal positive symptoms. This similarity further suggests that both SPD and 22q11DS can be seen as prodromal groups. It also may suggest that these groups share common biological and/or environmental mechanisms that lead to the presence of subthreshold positive symptoms of psychosis. It is possible that genes on the 22q11.2 chromosomal region are involved in these mechanisms.

Figure 3 also suggests a trend toward greater negative symptoms for the 22q11DS group that is partially substantiated by the covariance analyses. However, contrasts for the negative symptom domain in the ANCOVA models only reliably achieved

significance after variability due to the control v. combined clinical groups had been accounted for. Scores in this domain assess social, emotional, and academic/vocational functioning, as well as richness of ideas. Thus, these questions tap some of the same areas as do the anxious/depressed, withdrawn, and social problems scales on the CBCL, all areas in which the SPD group showed more abnormal scores than the 22q11DS group. It is possible that the myriad physical and learning problems associated with the 22q11.2 deletion affect individual performance in such a way that they are picked up on the SIPS, but not on the CBCL. It is also possible that the presence of these additional problems in living lead to more distress in these individuals, making them more susceptible to problems with mood and motivation. While these negative symptoms results are not consistent enough to make strong conclusions, this pattern of results suggests that comparisons of negative symptoms in different samples at risk for psychosis may be a worthwhile pursuit.

Conversely, the two clinical groups did not differ on general or disorganized symptom scores, though both had higher scores than controls. The disorganized symptom scale assesses odd behavior, appearance, and thinking, as well as trouble with focus, attention, and personal hygiene. The general scale taps sleep disturbance, dysphoric mood, motor disturbances, and impaired tolerance to stress. Again, the congruence in symptoms in these domains suggests that individuals selected solely on the basis of their prodromal or schizotypal symptoms show profiles similar to those selected based on the presence of the 22q11.2 genetic deletion. Although these results might appear inconsistent with the CBCL findings that the SPD group had higher attention problems and anxious/depressed scores than 22q11DS subjects, it is again important to

note that the parent ratings obtained by the CBCL are based on their non-clinical observations of subjects on a regular basis and in a variety of contexts. Thus, the behavioral phenomena that influence parents' ratings of attention problems and anxiety/depression may not be as readily observed in the clinical setting. Nonetheless, the fact that the two clinical groups did not differ on the SIPS general and disorganized symptom scales is consistent with extensive data indicating that both groups are at elevated risk for psychosis

Overall, although there were some differences between the clinical groups in mean ratings for the SIPS and CBCL scores, the SPD and 22q11DS groups show remarkably similar patterns of symptoms. On the SIPS domain factor scores and non-externalizing CBCL scores, the two clinical groups show roughly parallel patterns of elevations when compared to the control group. Together, these findings suggest a remarkable overlap in the prodromal and behavioral symptom profiles of the 22q11DS and SPD groups. This congruence in symptom profiles between the two groups suggests two conclusions. First, it points to the importance of further research on etiological distinctions between the two groups. To date, very little research has been done comparing the biobehavioral characteristics of psychosis as it is manifested in 22q11DS versus non-22q-SZ patients. Results of the current study suggest that the psychosis prodrome in these groups is likely to be similar, with substantive differences seen only in the severity of positive and possibly negative symptoms. This suggests that the genetic mechanisms that lead to the psychiatric phenomenology in 22q11DS may overlap with those responsible for the profile seen in SPD. In other words, genes in the 22q11.2 chromosomal region may confer risk for the development of psychosis in both SPD and

22q11DS patients. Second, this conclusion is also consistent with the evidence that the symptom profiles are similar in 22q-SZ and non-22q-SZ (Murphy et al., 1999; Bassett et al., 2003).

Diagnostic group differences in prodromal syndromes

Given the elevated risk for axis I psychosis in both SPD and 22q11DS, it was hypothesized that at least 25% of individuals in the 22q11DS and SPD groups would meet criteria for at least one prodromal syndrome.

Results are consistent with this prediction. Because data on the duration of symptoms were not available for all participants, the rates of prodromal syndromes were assessed by focusing only on the symptom severity criteria. According to these criteria, 61.5% of the SPD group and 58.9% of the 22q11DS group met criteria for either Attenuated Positive Symptom Syndrome (APS) or Brief Intermittent Psychotic Syndrome (BIPS). Thus, according to these estimates, a similarly large proportion of 22q11DS and SPD individuals meet criteria for a prodromal syndrome. This accords well with the results of this SIPS analysis, which showed that the groups had very similar patterns of prodromal symptoms, although the SPD group had a baseline increase in positive symptom severity and trend-level decrease in negative symptoms compared to the 22q11DS group.

As noted, past research using the SIPS/SOPS indicates that the conversion rate to axis I psychosis within 2 to 3 years from baseline ranges from 30 to 40% in those who meet criteria for the prodrome (Miller et al., 2003; Yung et al., 2003; Lemos et al., 2006; Cannon et al., 2008). Thus, if 30 to 40% of those in the present study who meet

prodromal criteria eventually convert to psychosis, the rate of psychotic outcomes in the SPD and 22q11DS groups would be 15.385 to 24.615% and 15.625 to 25%, respectively. These figures are at the lower end of the range of estimated eventual rates of psychosis in the two groups.

Ten controls (19.6%) also met symptom criteria for one of the prodromal syndromes. Given that the base rate of Schizophrenia in the general population is only approximately 1% and approximately 30 to 40% of those classified as prodromal develop illness, these estimates seem high. However, there is a growing literature on the presence of 'psychotic-like' experiences in healthy members of the general population. This literature suggests that as much as 13 to 38% of late adolescent controls report prodromal level delusions (Morgan et al., 2009; Rossler et al., 2007; Loewy et al., 2007). In summarizing this literature, Van Os and colleagues (2009) conclude that these experiences are transitory and disappear over time in 75-90% of cases. It therefore appears that the present counterintuitive findings in the healthy control group actually converge with previous reports. Moreover, the results raise salient questions about the validity of the SIPS/SOPS criteria if applied to healthy or non-clinical populations.

Combining POPS and prodromal syndrome ratings (BIPS and APS) yields a total of 71.8% of the SPD group and 61.77% of the 22q11DS group that fall into one of the three syndromes. This is also consistent with the evidence that the SIPS/ SOPS over-estimates the rate of eventual psychosis in these groups.

The fact that the SIPS/SOPS yields inflated estimates of the psychosis prodrome relative to actual rates of psychosis, points to the importance of further predictive research. In fact, several research groups are pursuing such endeavors, with the aim of

enhancing positive predictive power by combining the SIPS/SOPS with other measures, both behavioral and biological. The findings of these investigations will be critical for designing the next generation of prevention studies. More specifically, before preventive interventions can be applied, individuals at risk for psychosis must be identified with greater precision.

Limitations

The chief limitation of the present study was the small sample size, particularly in the demographic-matched analyses. Power analyses indicated that, in the covariance analyses, the current study's size precluded it from detecting significant effects of small magnitudes. The demographic-matching analyses used substantially smaller samples and thus reduced power for detecting moderate effect sizes. In some analyses, this contributed to the violation of important assumptions that underlie parametric tests. On the other hand, because of the small baseline rate of these risk conditions, especially 22q11DS, subject ascertainment and recruitment is challenging. Thus, the sample sizes in the present study are in the range of many previous reports on both 22q11DS and SPD, highlighting the inherent difficulties of studying such low base rate conditions.

The second limitation concerns the age differences among the groups. This is largely a function of the fact that the recruitment of 22q11DS subjects is the most challenging, as genotyping must be conducted to verify the presence of the risk condition. Further, it is less common than SPD. Thus, a much broader age-range is represented in the 22q11DS group, which made it difficult to match subjects on demographic characteristics. Finally, although the current study attempted to match the experimental procedures used to collect data on 22q11DS and SPD, the two groups were recruited and

run in different locations by different researchers. It is possible that this introduced measurement confounds that cannot currently be accounted for.

Summary

Despite the limitations noted above, the present study has revealed some areas of phenomenological overlap, as well as divergence, between the SPD and 22q11DS groups. With respect to behavioral problems tapped by the CBCL, the SPD group manifests a significantly higher rate of externalizing problems, as well as more subtle differences in the severity of other behavior problems. In light of the fact that externalizing problems play no role in the diagnosis of either disorder, this finding is of particular interest. Past studies of premorbid behavioral problems in Schizophrenia have revealed elevations in both internalizing and externalizing behavioral problems on the CBCL (Neumann & Walker, 1995). In future research, the association of externalizing behavior problems with later psychosis in 22q11DS should be explored. This may be a dimension that distinguishes premorbid dysfunction in 22q11DS from other groups at risk for psychosis.

The results of the current investigation also shed new light on prodromal syndromes in SPD and 22q11DS. Indeed, the phenomenology of the prodromal syndrome in these two groups is more similar than different; the risk-groups profiles, relative to controls, are highly convergent. Given that previous data indicate that the two groups have comparable risks for conversion to Axis I psychotic disorders, these findings suggest that it is reasonable to utilize the SIPS/SOPS in studies of the prodrome in 22q11DS patients.

There were also some notable differences between the SPD and 22q11DS groups. In particular, the SPD group showed more severe positive symptoms and a trend toward fewer negative symptoms than the 22q11DS group. In future studies, it will be of interest to determine whether the relative power of the various prodromal symptom ratings to predict psychotic outcomes varies for the two risk groups. It may be, for example, that the ratings on the general and disorganized symptom domains are less predictive of psychotic outcome in the 22q11DS patients because they tap deficits that are not specific to the psychosis prodrome.

With the burgeoning interest in the prevention of psychotic disorders, researchers are intensifying their focus on the more precise identification of prodromal states. Given the phenomenological heterogeneity among psychotic disorders, it is likely that multiple prodromal syndrome subtypes will emerge. The present study suggests that these subtypes may involve differences in the severity of positive and negative prodromal symptoms, as well as externalizing behavior problems and role functioning abilities. Further, the differences observed between SPD and the 22q11DS contribute to our understanding of the phenotypic characteristics that may be influenced by genes in the 22q11.2 chromosomal region. Important questions yet to be addressed include: What genes are involved in the internalizing problems and negative symptoms observed in the 22q11DS patients? What genes are involved in the 22q11DS cognitive deficits, and what role do these genes play in triggering or modifying risk for psychosis?

References

Achenbach, T.M., Rescorla, L.A. (2001). Manual for the ASEBA school-age forms & profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Adams, K.M., Brown, G.G., Grant, I. (1985). Analysis of covariance as a remedy for demographic mismatch of research subject groups: some sobering simulations. J Clin Exp Neuropsychol, 7(4), 445-62.

Akritas, M.G., Arnold, S.F., Du Y. (2000). Nonparametric models and methods for nonlinear analysis of covariance. Biometrika, 87(3), 507-526.

Allen, D.N., Kelley, M.E., Miyatake, R.K., Gurklis, J.A., van Kammen, D.P. (2001). Confirmation of a Two-Factor Model of Premorbid Adjustment in Males with Schizophrenia. Schizophrenia Bulletin, 27(1), 39-46.

Amati, F., Biancolella, M., Farcomeni, A., Giallonardi, S., Bueno, S., Minella, D., Vecchione, L., Chillemi, G., Desideri, A., Novelli, G. (2007). Dynamic changes in gene expression profiles of 22q11 and related orthologous genes during mouse development. Gene, 391, 91-102.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR (fourth edition, text revision). Washington DC: American Psychiatric Association, 2000

Antonarakis, S.E., Pulver, A.E., Housman, D.E. (1995). Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. Proc Natl Acad Sci, 92, 7612-7616.

Arinami, T. (2006). Analyses of the associations between the genes of 22q11 deletion syndrome and Schizophrenia. Journal of Human Genetics, 51, 1037-1045.

Arnold, P.D., Siegel-Bartelt, J., Cytrynbaum Teshima, I., Schachar, R. (2001). Velo-cardio-facial syndrome: Implications of microdeletion 22q11 for Schizophrenia and mood disorders. American Journal of Medical Genetics (Neuropsychiatric Genetics), 105, 354-362.

Asarnow, J.R. (2005). Childhood-Onset Schizotypal Disorder: AFollow-Up Study and Comparison with Childhood-Onset Schizophrenia. Journal of Child and Adolescent Psychopharmacology, 15(3), 395-402.

Baker, K.D., Skuse, D.H. (2005). Adolescents and young adults with 22q11 deletion syndrome: psychopathology in an at-risk group. British Journal of Psychiatry, 186, 115-120.

Bassett, A.S., Hodgkinson, K., Chow, E.W.C., Correia, S., Scutt, L.E., Weksberg, R. (1998). 22q11 deletion syndrome in adults with Schizophrenia. American Journal of Medical Genetics (Neuropsychiatric Genetics), 81, 328-337.

Bassett, A.S., Chow, E.W.C. (1999). 22q11 Deletion Syndrome: A Genetic Subtype of Schizophrenia. Biological Psychiatry, 46, 882-891.

Basset, A.S., Chow, E.W.C., AbdelMalik, P., Gheorghiu, M., Husted, J., Weksberg, R. (2003). The Schizophrenia phenotype in 22q11 deletion syndrome. American Journal of Psychiatry, 160, 1580-1586.

Bearden, C.E., van Erp, T.G.M., Monterosso, J.R., Simon, T.J., Glahn, D.C., Saleh, P.A., Hill, N.M., McDonald-McGinn, D.M., Zackal. E,, Emanuel, B.S., Cannon, T.D.

(2004). Regional brain abnormalities in 22q11.2 deletion syndrome: Association with cognitive abilities and behavioral symptoms. Neurocase, 10(3), 198-206.

Bergman, A.J., Harvey, P.D., Lees Roitman, S., Mohs, R.C., Marder, D., Silverman, J.M., Siever, L.J. (1998). Verbal learning and memory in schizotypal personality disorder. Schizophrenia Bulletin, 24(4), 635-641.

Berrettini, W.H. (2000). Are Schizophrenia and bipolar disorders related? A review of family and molecular studies. Biological Psychiatry, 48(6), 531-538.

Birkett, P., Sigmundsson, T., Sharma, T., Toulopoulou, T., Griffiths, T.D., Revely, A., Murray, R. (2007). Reaction Time and Sustained Attention in Schizophrenia and its Genetic Predisposition. Schizophrenia Research, 95, 76-85.

Boot, E., Booij, J., Zinkstok, J., Abeling, N., de Haan, L., Baas, F., Linszen, D., van Amelsvoort, T. (2008). Disrupted dopaminergic neurotransmission in 22q11 deletion syndrome. Neuropsychopharmacology, 33(6), 1252-1258.

Braff, D.L., Light, G.A. (2005). The use of neurophysiological endophenotypes to understand the genetic basis of Schizophrenia. *Diologues in C,linical Neuroscience*, 7(2), 125-135.

Braver, T.S., Barch, D.M., Cohen, J.D. (1999). Cognition and control in Schizophrenia: a computational model of dopamine and prefrontal function. Biological Psychiatry, 46(3), 312-328.

Cadenhead, K.S., Braff, D,L (2002). Endophenotyping schizotypy: a prelude to genetic studies within the Schizophrenia spectrum. *Schizophrenia Research*, 54, 47-57.

Cadenhead, K.S., Perry, W., Shafer, K., Braff, D.L. (1999). Cognitive functions in schizotypal personality disorder. Schizophrenia Research, 37, 123-132.

Cannon, M., Jones, P., Huttunen, M.O., Tanskanen, A., Huttunen, T., Rabe-Hesketh, S., Murray, R.M. (1999). School performance in Finnish children and later development of Schizophrenia: a population-based longitudinal study. Arch Gen Psychiatry, 56, 457–463.

Cannon, T.D., Mednick, S.A., Parnas, J., Schulsinger, F., Praestholm, J., Vestergaard, A. (1994). Developmental brain abnormalities in the offspring of Schizophrenia mothers. II. Structural brain characteristics of Schizophrenia and schizotypal personality disorder. Archives of General Psychiatry, 51(12), 955-962.

Cannon, T.D., Cadenhead, K., Cornblatt, B., Woods, S.W., Addington, J., Walker, E., Seidman, L.J., Perkins, D., Tsuang, M., McGlashan, T., Heinssen, R. (2008). Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Archives of General Psychiatry, 65(1), 28-37.

Chow, E.W.C., Watson, M., Young, D.A., Bassett, A.S. (2006). Neurocognitive profile in 22q11 deletion syndrome and Schizophrenia. Schizophrenia Research, 87, 270-278.

Corcoran, C., Davidson, L., Sills-Shahar, R., Nickou, C., Malaspina, D., Miller, T., McGlashan, T. (2004). A qualitative research study of the evolution of symptoms in individuals identified as prodromal to psychosis. Psychiatric Quarterly, 74(4), 313-332.

Cornblatt, B.A., Auther, A.M., Niendam, T., Smith, C.W., Zinberg, J., Bearden, C.E., Cannon, T.D. (2007). Preliminary findings for two new measures of social and role functioning in the prodromal phase of Schizophrenia. Schizophrenia Bulletin, 33(3), 688-702.

Cornblatt, B.A., Lencz, T., Smith, C.W., Correll, C.U., Auther, A.M., Nakayama, E. (2003). The Schizophrenia prodrome revisited: A neurodevelopmental perspective. Schizophrenia Bulletin, 29(4), 633-651.

Debbane, M., Glaser, B., David, M.K., Feinstein, C., Eliez, S. (2006). Psychotic symptoms in children and adolescents with 22q11.2 deletion syndrome: Neuropsychological and behavioral implications. Schizophrenia Research, 84, 187-193.

Dickey, C.C., McCarley, R.W., Voglmaier, M.M., Niznikiewicz, M.A., Seidman, L.J., Hirayasu, Y., Fischer, I., Teh., E.K., Van Rhoads, R., Jakab, M., Kikinis, R., Jolesz, F.A., Shenton, M.E. (1999). Schizotypal personality disorder and MRI abnormalities of temporal gray matter. Biological Psychiatry, 45, 1393-1402.

Dickey, C.C., McCarley, R.W., Shenton, M.E. (2002). The brain in schizotypal personality disorder: a review of structural MRI and CT findings. Harv Rev Psychiatry, 10(1), 1-15.

Dickey, C.C., McCarley, R.W., Xu, M.L., Seidman, L.J., Voglmaier, M.M., Niznikiewicz, M.A., Connor, E., Shenton, M.E. (2007). MRI abnormalities of the hippocampus and cavum septi pellucidi in females with schizotypal personality disorder. Schizophrenia Research, 89(1-3), 49-58.

Diforio, D., Walker, E.F., Kestler, L.P.(2000). Executive functions in adolescents with schizotypal personality disorder. Schizophrenia Research, 42(2), 125-34.

Downhill, J.E., Buchsbaum, M.S., Hazlett, E.A., Barth, S., Lees Roitman, S., Nunn, M., Lekarev, O., Wei, T., Shihabuddin, L., Mitropoulou, V., Silverman, J., Siever, L.J. (2001). Temporal lobe volume determined by magnetic resonance imaging in

schizotypal personality disorder and Schizophrenia. Schizophrenia Research, 48, 187-199

Dufour, F., Schaer, M., Debbane, M., Farhoumand, R., Glaser, B., Eliez, S. (2008). Cingulate gyral reductions are related to low executive functioning and psychotic symptoms in 22q11.2 deletion syndrome. Neuropsychologia, 46, 2986-2992.

Egan, M.F., Goldberg, T.E., Kolachana, B.S., Callicott, J.H., Mazzanti, C.M., Straub, R.E., Goldman, D., Weinberger, D.R. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for Schizophrenia. Proceedings of the National Academy of Sciences, 98(12), 6917-22.

Eliez, S., Schmitt, J.E., White, C.D., Reiss, A.L. (2000). Children and adolescents with velocardiofacial syndrome: a volumetric MRI study. American Journal of Psychiatry, 157(3), 409-415.

Ekstrom, M. Lykke Mortensen, E., Sorensen, H.J., Mednick, S.A. (2006). Premorbid personality in Schizophrenia spectrum: a prospective study. Nord J Psychiatry, 60(5), 417-422.

Feinstein, C., Eliesz, S., Blasey, C., Reiss, A.L. (2002). Psychiatric disorders and behavioral problems in children with velocardiofacial syndrome: usefulness as phenotypic indicators of Schizophrenia risk. Biological Psychiatry, 51, 312-318.

Fine, S.E., Weissman, A., Gerdes, M., Pinto-Martin, J., Zackai, E.H., McDonald-McGinn, D.M., Emmanuel, B.S. (2005). Autistic spectrum disorders and symptoms in children with molecularly confirmed 22q11.2 deletion syndrome. J Autism Dev Disord. 35:461-470. *cited from Arinami, T. (2006). Analyses of the*

associations between the genes of 22q11 deletion syndrome and Schizophrenia. Journal of Human Genetics, 51, 1037-1045.

Gerdes, M., Solot, C., Wang, P.P., Moss, E., LaRossa, D., Randall, P., Goldmuntz, E., Clark, B.J. 3rd, Driscoll, D.A., Jawad, A., Emanuel, B.S., McDonald-McGinn, D.M., Batshaw, M.L., Zackai, E.H. (1999). Cognitive and behavior profile of preschool children with chromosome 22q11.2 deletion. Am J Med Genet, 85(2), 127-133.

Geyer, M.A., Krebs-Thomson, K., Braff, D.L., Swerdlow, N.R. (2001). Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in Schizophrenia: A decade in review, *Psychopharmacology,* 156, 117–154.

Gogos, J.A., Santha, M., Takacs, Z., Beck, K.D., Luine, V., Lucas, L.R., Nadler, J.V., Karayiorgou, M. (1999). The gene encoding praline dehydrogenase modulates sensorimotor gating in mice. Nature Genetics, 21(4), 434-439.

Goldberg, R., Motzkin, B., Marion, R., Scambler, P.J., Shprintzen, R.J. (1993). Velo-cardio-facial syndrome: a review of 120 patients. American Journal of Medical Genetics, 45, 313-319. *cited from Gothelf, D., Frisch, A., Munitz, H., Rockah, R., Laufer, N., Mozes, T., Hermesh, H., Weizman, A., Frydman, M. (1999). Clinical characteristics of Schizophrenia associated with velo-cardio-facial syndrome. Schizophrenia Research, 35, 105-112.*

Golding-Kushner, K.J., Weller, G., Shprintzen, R.J. (1985). Velo-cardio-facial syndrome: Language and psychological profiles. Journal of Craniofacial Genetics and Developmental Biology, 5, 259-266.

Goodship, J., Cross, I., LiLing, J., Wren, C. (1998). A population study of chromosome 22q11 deletions in infancy. Arch Dis Child, 79, 348-351.

Gothelf, D., Frisch, A., Munitz, H., Rockah, R., Laufer, N., Mozes, T., Hermesh, H., Weizman, A., Frydman, M. (1999). Clinical characteristics of Schizophrenia associated with velo-cardio-facial syndrome. Schizophrenia Research, 35, 105-112.

Gothelf, D., Frisch, A., Munitz, H., Rockah, R., Laufer, N., Mozes, T., Hermesh, H., Weizman, A., Frydman, M. (1999b). Schizophrenia Research, 35, 105-112.

Gothelf, D., Penniman, L., Gu, E., Eliez, S., Reiss, A.L. (2007). Developmental trajectories of brain structure in adolescents with 22q11.2 deletion syndrome: A longitudinal study. Schizophrenia Research, 96, 72-81.

Gothelf, D., Feinstein, C., Thompson, T., Gu, E., Penniman, L., Van Stone, E., Kwon, H., Eliez, S., Reiss, A.L. (2007b). Risk factors for the emergence of psychotic disorders in adolescents with 22q11.2 deletion syndrome. American Journal of Psychiatry, 164(4), 663-669.

Gottesman, I.I., Gould, T.D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. American Journal of Psychiatry, 160(4), 636-645.

Goulding, M.D., Chalepakis, G., Deutsh, U., Erselius, J.R., Gruss, P. (1991). Pax-3, a novel murine DNA binding protein expressed during early neurogenesis. EMBO J, 10, 1135-1147. *cited from Amati, F., Biancolella, M., Farcomeni, A., Giallonardi, S., Bueno, S., Minella, D., Vecchione, L., Chillemi, G., Desideri, A.,*

Novelli, G. (2007). Dynamic changes in gene expression profiles of 22q11 and related orthologous genes during mouse development. Gene, 391, 91-102.

Gur, R.E., Nimgaonkar, V.L., Almasy, L., Calkins, M.E., Ragland, J.D., Pogue-Geile, M.F., Kanes, S., Blanqero, J., Gur, R.C. (2007). Neurocognitive Endophenotypes in a Multiplex Multigenerational Family Study of Schizophrenia. American Journal of Psychiatry, 164(5), 813-819.

Harrison, P.J., Weinberger, D.R. (2005). Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Molecular Psychiatry, 10, 40–68.

Harvey, P.D., Bellack, A.S. (2009). Toward a terminology for functional recovery in Schizophrenia: Is functional remission a viable concept? *Schizophrenia Bulletin*, 35(2), 300-306.

Hazlett, E.A., Buchsbaum, M.S., Haznedar, M.M., Newmark, R., Goldstein, K.E., Zelmanova, Y., Glanton, C.F., Torosjan, Y., New, A.S., Lo, J.N., Mitropoulou, V., Siever, L.J. (2008). Cortical gray and white matter volume in unmedicated schizotypal and Schizophrenia patients. Schizophrenia Research, 101, 111-123.

Heineman–De Boer, J.A., Van Haelst, M.J., Cordia-De Haan, M., Beemer, F.A. (1999). Behaviour problems and personality aspects of 40 children with velo-cardio-facial syndrome. Genetic Counseling, 10, 89-93. *cited from Arnold, P.D., Siegel-Bartelt, J., Cytrynbaum Teshima, I., Schachar, R. (2001). Velo-cardio-facial syndrome: Implications of microdeletion 22q11 for Schizophrenia and mood disorders. American Journal of Medical Genetics (Neuropsychiatric Genetics), 105, 354-362.*

Heinrichs, R.W., Zakzanis, K.K. (1998). Neurocognitive deficit in Schizophrenia: a quantitative review of the evidence. Neuropsychology, 12(3), 426-445.

Henry, J.C., van Amelsvoort, T., Morris, R.G., Owen, M.J., Muphry, D.G.M., Muphy, K.C. (2002). An investigation of the neuropsychological profile in adults with velo-cardio-facial syndrome (VCFS). Neuropsychologia, 40, 471-478.

Horan, W.P., Blanchard, J.J., Clark, L.A., Green, M.F. (2008). Affective traits in Schizophrenia and schizotypy. Schizophrenia Bulletin, 34(5), 856-874.

Horan, W.P., Reise, S.P., Subotnik, K.L., Ventura, J., Nuechterlien, K.H. (2008). The validity of Psychosis Proneness Scales as vulnerability indicators in recent-onset Schizophrenia patients. Schizophrenia Research, 100(1-3), 224-236.

Horowitz, A., Shifman, S., Rivlin, N., Pisante, A., Darvasi, A. (2005). A survey of the 22q11 microdeletion in a large cohort of Schizophrenia patients. Schizophrenia Research, 73, 263-267.

Ivanov, D., Kirov, G., Norton, N., Williams, H.J., Williams, N.M., Nikolov, I., Tzwetkova, R., Stambolova, S.M., Murphy, K.C., Toncheva, D., Thapar, A., O'Donovan, M.C., Owen, M.J. (2003) Chromosome 22q11 deletions, velo-cardio-facial syndrome and early-onset psychosis; Molecular genetic study. British Journal of Psychiatry, 183, 409-413.

Jones P, Rodgers B, Murray R, Marmot M. Child developmental risk factors for adult Schizophrenia in the British 1946 birth cohort. Lancet, 1994, 344:1398–1402.

Karayiorgou, M., Morris, M.A., Morrow, B., Shprintzen, R.J., Goldberg, R., Borrow, J., Gos, A., Nestadt, G., Wolyniec, P.S., Lasseter, V.K., Eisen, H., Childs, B., Kazazian, H.H., Kucherlapati, R., Kiley-Brabeck, K., Sobin, C. (2006). Social

skills and executive function deficits in children with the 22q11 deletion syndrome. Applied Neuropsychology, 13(4), 258-268.

Kendler, K.S., Gruenberg, A.M., Strauss, J.S. (1981). An independent analysis of the Copenhagen sample of the Danish adoption study of Schizophrenia. II. The relationship between schizotypal personality disorder and Schizophrenia. Arch Gen Psychiatry, 38(9), 982-984.

Kendler, K.S., Neale, M.C., Walsh, D. (1995). Evaluating the Spectrum Concept of Schizophrenia in the Roscommon Family Study. American Journal of Psychiatry, 152(5), 749-54.

Keppel, G., Wickens, T.D. (2004). Design and analysis; A researcher's handbook (4th ed.). Upper Saddle River, New Jersey: Pearson Prentice Hall.

Kiley-Brabeck, K., Sobin, C. (2006). Social skills and executive function deficits in children with the 22q11 Deletion Syndrome. Applied Neuropsychology, 13(4), 258-268.

Kumari, V., Das, M., Zachariah, E., Ettinger, U., Sharma, T. (2005). Reduced prepulse inhibition in unaffected siblings of Schizophrenia patients, *Psychophysiology*, 42, 588–594.

Lajiness-O'Neill, R., Beaulieu, I., Asamoah, A., Titus, J.B., Bawle, E., Ahmad, S., Kirk, J.W., Pollack, R. (2006). The neuropsychological phenotype of velocardiofacial syndrome (VCFS): Relationship to psychopathology. Archives of Clinical Neuropsychology, 21, 175-184.

Lee, S.J., Yoo, S.Y., Kang, D.H., Lee, K.J., Ha, T.H., Wee, W., Lee, A.R., Kim, N.S., Kwon, J.S. (2008). Potential vulnerability markers within the affective domain in

subjects at genetic and clinical high risk for Schizophrenia. Psychopathology, 41(4), 236-244.

Leech, N.L., Caplovitz Barrett, K., Morgan, G.A. (2004). SPSS for Intermediate Statistics: Use and Interpretation; Secong Edition. Mahwah, Jew Jersey: Routledge.

Lemos, S., Vallina, O., Fernandez, P., Ortega, J.A., Garcia, P., Gutierrez, A., Bobes, J., Garcia, A., Miller, T. (2006). Predictive validity of the scale of prodromal symptoms (SOPS). Actas Esp Psiquiatr, 34(4), 216-223.

Lewandowski, K.E., Shashi, V., Berry, P.M., Kwapil, T.R. (2007). Schizophrenic-like neurocognitive deficits in children and adolescents with 22q11 deletion syndrome. American Journal of Medical Genetics Part B, Neuropsychiatric Genetics, 144(1), 27-36.

Lewis, C.M., Levinson, D.F., Wise, L.H., DeLisi, L.E., Straub, R.E., Hovatta, I., Williams N.M., Schwab, S.G., Pulver, A.E., Faraone, S.V., Brzustowicz, L.M., Kaufmann, C.A., Garver, D.L., Gurling, H.M., Lindholm, E., Coon, H., Moises, H.W., Byerley, W., Shaw, S.H., Mesen, A., Sherrington, R., O'Neill, F.A., Walsh, D., Kendler, K.S., Ekelund, J., Paunio, T., Lönnqvist, J., Peltonen, L., O'Donovan, M.C., Owen, M.J., Wildenauer, D.B., Maier, W., Nestadt, G., Blouin, J.L., Antonarakis, S.E., Mowry, B.J., Silverman, J.M., Crowe, R.R., Cloninger, C.R., Tsuang, M.T., Malaspina, D., Harkavy-Friedman, J.M., Svrakic, D.M., Bassett, A.S., Holcomb, J., Kalsi, G., McQuillin, A., Brynjolfson, J., Sigmundsson, T., Petursson, H., Jazin, E., Zoëga, T., Helgason, T. (2003). Genome scan meta-

analysis of Schizophrenia and bipolar disorder, part II: Schizophrenia. Am J Hum Genet, 73, 34–48.

Little, R.J., An, H., Johanns, J., Giordani, B. (2000). A comparison of subset selection and analysis of covariance for the adjustment of confounders. Psychol Methods, 5(4), 459-76.

Loewy, R.L., Bearden, C.E., Johnson, J.K., Raine, A., Cannon, T.D. (2005). The prodromal questionnaire (PQ): preliminary validation of a self-report screening measure for prodromal and psychotic syndromes. Schizophrenia Research, 77(2-3), 141-149.

Loewy, R.L., Johnson, J.K., Cannon, T.D. (2007). Self-report of attenuated psychotic experiences in a college population. Schizophrenia Research, 93, 144-151.

Ma, G., Shi, Y., Tang, W., He, Z., Huang, K., Li, Z., He, G., Feng, G., Li, H., He, L. (2007) An association study between the genetic polymorphisms within TBX1 and Schizophrenia in the Chinese population. Neuroscience Letters, 425(3), 146-150.

MacDonald, A.W., Shulz, S.C. (2009). What we know: Findings that every theory of Schizophrenia should explain. *Schizophrenia Bulletin*, 35(3), 493-508.

Maier, W. (2008). Common risk genes for affective and schizophrenic psychoses. Eur Arch Psychiatry Clin Neurosci, 258(S2), 37-40.

Maynard, T.M., Sikich, L., Lieberman, J.A., LaMantia, A.S. (2001). Neural development, cell-cell signaling, and the "two-hit" hypothesis of Schizophrenia. Schizophrenia Bulletin, 27, 457-476.

Maynard, T.M., Haskell, G.T., Lieberman, J.A., LaMantia, A.S. (2002). 22q11 DS: genomic mechanisms and gene function in DiGeorge/velocardiofacial syndrome. Journal of Developmental Neuroscience, 20, 407-419.

Maynard, T.M., Haskell, G.T., Peters, A.Z., Sikich, L., Lieberman, J.A., LaMantia, A.S. (2003). A comprehensive analysis of 22q11 gene expression in the developing adult brain. PNAS, 100(24), 14433-14438.

McClure, M.M., Romero, M.J., Bowie, C.R., Reichenberg, A., Harvey, P.D., Siever, L.J. (2007). Visual-spatial learning and memory in schizotypal personality disorder: continued evidence for the importance of working memory in the Schizophrenia spectrum. Archives of clinical neuropsychology, 22, 109-116.

McClure, M.M., Barch, D.M., Flory, J.D., Harvey, P.D., Siever, L.J. (2008). Context processing in schizotypal personality disorder: evidence of specificity of impairment to the Schizophrenia spectrum. Journal of Abnormal Psychology, 117(2), 342-354.

McGlashan, T.H., Miller, T.J., Woods, S.W., Rosen, J.L., Hoffman, R.E., Davidson, L. (2001), Structured Interview for Prodromal Syndromes (SIPS), Yale University, New Haven (2001).

McGorry, P.D., McFarlane, C., Patton, G.C., Bell, R., Hibbert, M.E., Jackson, H.J., Bowes, G. (1995). The prevalence of prodromal features of Schizophrenia in adolescence: A preliminary survey. Acta Psychiatrica Scandinavica, 92(4), 241-249.

McGorry, P.D., Killackey, E., Yung, A. (2008). Early intervention in psychosis: concepts, evidence and future directions. World Psychiatry, 7(3), 148-156.

McGrath, J., Saha, S., Chant, D., Welham, J. (2008). Schizophrenia: A concise overview of incidence, prevalence, and mortality. Epidemiologic Reviews, 30, 67-76.

Meyer, S.E., Bearden, C.E., Lux, S.R., Gordon, J.L., Johnson, J.K., O'Brien, M., Niendam, T.A., Loewy, R.L., Ventura, J., Cannon, T.D. (2005). The psychosis prodrome in adolescent patients viewed through the lens of DSM-IV. Journal of Child and Adolescent Psychopharmacology, 15(3), 434-451.

Miller, G.A., Chapman, J.P. (2001). Misunderstanding analysis of covariance. Journal of Abnormal Psychology, 110(1), 40-48.

Miller, T.J., McGlashan, T.H., Rosen, J.L., Cadenhead, K., Ventura, J., McFarlane, W., Perkins, D.O., Pearlson, G.D., Woods, S.W. (2003). Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophrenia Bulletin, 29(4), 703-715.

Mitropoulou, V., Harvey, P.D., Maldari, L.A., Moriarty, P.J., New, A.S., Silverman, J.M., Siever, L.J. (2002). Neuropsychological performance in schizotypal personality disorder: evidence regarding diagnostic specificity. Biological psychiatry, 52, 1175-1182.

Mittal, V.A., Saczawa, M.E., Walder, D., Willhite, R., Walker, E.F. (2008) Prenatal exposure to viral infection and conversion among male adolescents at high-risk for psychotic disorders. Schizophrenia Research, 99(1-3), 375-376.

Mittal, V.A., Tessner, K.D., Trottman, H.D., Esterberg, M. Dhrub, S.H., Simeonova, D.I., McMillan, A.L., Murphy, E., Saczawa, M.E., Walker, E.F. (2007). Movement

abnormalities and the progression of prodromal symptomatology in adolescents at risk for psychotic disorders. Journal of Abnormal Psychology, 116(2), 260-267.

Morgan, C., Fisher, H., Hutchinson, G., Kirkbride, J., Craig, T.K., Morgan, K., Dazzan, P., Boydell, J., Doody, G.A., Jones, P.B., Murray, R.M., Leff, J., Fearon, P. (2009). Ethnicity, social disadvantage and psychotic-like experiences in a healthy population based sample. Acta Psychiatr Scand, 119(3), 226-235.

Moriarty, P.J., Harvey, P.D., Mitropoulou, V., Granholm, E., Silverman, J.M., Siever, L.J. (2003). Reduced processing resource availability in schizotypal personality disorder: evidence from a dual-task CPT study. J Clin Exp Neuropsychol, 25(3), 335-47.

Moskvina, V., Craddock, N., Holmans, P., Nikolov, I., Pahwa, J.S., Green, E.; Wellcome Trust Case Control Consortium3, Owen MJ, O'Donovan MC (2009). Gene-wide analyses of genome-wide association data sets: evidence for multiple common risk alleles for Schizophrenia and bipolar disorder and for overlap in genetic risk. Mol Psychiatry, 14(3), 252-260.

Murphy, K.C., Owen, M.J. (1997). The behavioural phenotype in velo-cardio-facial syndrome. American Journal of Human Genetics, 61, A5.

Muphy, K.C., Jones, L.A., Owen, M.J. (1999). High rates of Schizophrenia in adults with velo-cardio-facial syndrome. Archives of General Psychiatry, 56(10), 940-945.

Muphy, K.C., Owen, M.J. (2001). Velo-cardio-facial syndrome: a model for understanding the genetics and pathogenesis of Schizophrenia. British Journal of Psychiatry, 179, 397-402.

Murphy, K.C. (2002). Schizophrenia and velo-cardio-facial syndrome. The Lancet, 359, 426-430.

Neumann, C., & Walker, E. (1995). Developmental pathways to Schizophrenia: Behavioral subtypes. Journal of Abnormal Psychology, 104, 1-9.

Neumann, C.S., Walker, E.F. (1999). Motor dysfunction in schizotypal personality disorder. Schizophrenia Research, 38(2-3), 159-168.

Niklasson, L., Rasmussen, P., Oskarsdottir, S., Gillberg, C. (2005). Attention deficits in children with 22q.11 deletion syndrome. Developmental Medicine & Child Neurology, 47, 803-807.

Nordentoft, M., Thorup, A., Petersen, L., Ohlenschlaeger, J., Melau, M., Christensen, T.O., Krarup, G., Jorgensen, P., Jeppesen, P. (2006). Transition rates from schizotypal disorder to psychotic disorder for first-contact patients included in the OPUS trial. A randomized clinical trial of integrated treatment and standard treatment. Schizophrenia Research, 83, 29-40.

Olejnik, S.F., Algina, J. (1985). A Review of Nonparametric Alternatives To Analysis of Covariance. Evaluation Review, 9(1), 51-83.

Oskarsdottir, S., Belfrage, M., Sandstedt, E., Viggedal, G., Uvebrant, P. (2005). Disabilities and cognition in children and adolescents with 22q11 deletion syndrome. Developmental Medicine & Child Neurology, 47, 177-184.

Ott, S.L., Spinelli, S., Rock, D., Roberts, S., Amminger, G.P., Erlenmeyer-Kimling, L. (1998). The New York High-Risk Project: social and general intelligence in children at risk for Schizophrenia. Schizophrenia Research, 31(1), 1-11.

Owen, M.J., Craddock, N., O'Donovan, M.C. (2005). Schizophrenia: genes at last? TRENDS in genetics, 21(9), 518-525.

Papolos, D.F., Faedda, G.L., Veit, S., Goldberg, R., Morrow, B., Kucherlapati, R., Shprintzen, R.J. (1996). Bipolar spectrum disorders in patients diagnosed with velo-cardio-facial syndrome: does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? American Journal of Psychiatry, 153(12), 1541-1547.

Perala, J., Suvisaari, J., Saarni, S.I., Kuoppasalmi, K., Isometsa, E., Pirkola, S., Partonen, T., Huulio-Henriksson, A., Hintikka, J., Kieseppa, T., Harkanen, T., Koskinen, S., Lonnqvist, J. (2007). Lifetime prevalence of psychotic and bipolar I disorders in a general population. Archives of General Psychiatry, 64(1), 19-28.

Pfohl, B., Blum, N., Zimmerman, M. (1995). Structured interview for DSM-IV personality: DISP-IV. Washington DC: American Psychiatric Press.

Pulver, A.E., Nestadt, G., Goldberg, R., Shprintzen, R.J., Lamacz, M., Wolyniec, P.S., Morrow, B., Karayiorgou, M., Antonarakis, S.E., Housman, D., Kucheriapati, R. (1994). Psychotic illness in patients diagnosed with velo-cardio-facial syndrome and their relatives. Journal of Nervous and Mental Disease, 182, 476-478.

Reichenberg, A., Goldenberg, J. (2006). Self-reported mental health difficulties and subsequent risk for Schizophrenia in females: a 5-year follow-up cohort study. Schizophrenia Research, 82(2-3), 233-239.

Reichenberg, A., Weiser, M., Caspi, A., Knobler, H.Y., Lubin, G., Harvey, P.D., Rabinowitz, J., Davidson, M. (2006). Premorbid Intellectual Functioning and

Risk of Schizophrenia and Spectrum Disorders. Journal of Clinical and Experimental Neuropsychology, 28, 193-207.

Rockers, K., Ousley, O., Sutton, T., Schoenberg, E., Coleman, K., Walker, E., Cubells, J.F. (2009). Performance on the Modified Card Sorting Test and its relation to psychopathology in adolescents and young adults with 22q11.2 deletion syndrome. *Journal of Intellectual Disability Research,* 53(7), 665-676.

Rossler, W., Riecher-Rossler, A., Angst, J., Murray, R., Gamma, A, Eich, D., van Os, J., Gross, V.A. (2007). Psychotic experiences in the general population: a twenty-year prospective community study, Schizophrenia Research, 92(1-3), 1-14.

Ryan, A.K., Goodship, J.A., Wilson, D.I., Philip, N., Levy, A., Seidel, H. (1997). Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: A european collaborative study. Journal of Medical Genetics, 42, 1141-142. *cited from Gothelf D, Frisch A, Munitz H, Rockah R, Laufer N, Mozes T, Hermesh H, Weizman A, Frydman M (1999). Clinical characteristics of Schizophrenia associated with velo-cardio-facial syndrome. Schizophrenia Research, 35, 105-112.*

Saetre, P., Agartz, I., De Franciscis, A., Lundmark, P., Djurovic, S., Kähler, A., Andreassen, O.A., Jakobsen, K.D., Rasmussen, H.B., Werge, T., Hall, H., Terenius, L., Jönsson, E.G. (2008). Association between a disrupted-in-Schizophrenia 1 (DISC1) single nucleotide polymorphism and Schizophrenia in a combined Scandinavian case-control sample. Schizophr Res, 106(2-3), 237-241.

Schultze-Lutter, F., Ruhrmann, S., Hoyer, C., Klosterkotter, J., Leweke, F.M. (2007). The initial prodrome of Schizophrenia: different duration, different underlying deficits? Comprehensive Psychiatry, 48, 479-488.

Shifman, S., Bronstein, M., Sternfeld, M., Pisante, A., Weizman, A., Reznik, I., Spivak, B., Grisaru, N., Karp, L., Schiffer, R., Kotler, M., Strous, R.D., Swartz-Vanetik, M., Knobler, H.Y., Shinar, E., Yakir, B., Zak, N.B., Darvasi, A. (2004). COMT: A common susceptibility gene in bipolar disorder and Schizophrenia. American Journal of Medical Genetics Part B (Neuropsychiatric Genetics), 128B, 61-64.

Shifman, S., Levit, A., Chen, M.L., Chen, C.H., Bronstein, M., Weizman, A., Yakir, B., Navon, R., Darvasi, A. (2006). A complete genetic association scan of the 22q11 deletion region and functional evidence reveal an association between DGCR2 and Schizophrenia. Human Genetics, 120, 160-170.

Shprintzen, R.J., Goldberg, R.B., Lewin, M.L., Sidoti, E.J., Berkman, M.D., Argamaso, R.V., Young, D. (1978). A new syndrome involving cleft palate, cardiac anomalies, typical facies, and learning disabilities: velo-cardio-facial syndrome. Cleft Palate Journal, 15(1), 56-62.

Shprintzen, R.J., Goldberg, R., Golding-Kushner, K.J., Marion, R.W. (1992). Late-onset psychosis in the velo-cardio-facial syndrome (letter). American Journal of Medical Genetics, 42, 141-142. *cited from Muphy, K.C., Owen, M.J. (2001). Velo-cardio-facial syndrome: a model for understanding the genetics and pathogenesis of Schizophrenia. Brithis Journal of Psychiatry, 179, 397-402.*

Shprintzen, R.J. (2000). Velo-cardio-facial syndrome: a distinctive behavioral phenotype. Mental Retardation and Developmental Disabilities, 6, 142-147.

Siever, L.J., Rotter, M., Losonczy, M., Guo, S.L., Mitropoulou, V., Trestman, R., Apter, S., Zemishlany, Z., Silverman, J., Horvath, T.B., Davidson, M., Mohs, R., Davis, K.L. (1995). Lateral ventricular enlargement in schizotypal personality disorder. Psychiatry Research, 57, 109-118.

Siever, L.J., Davis, K.L. (2004). The pathophysiology of Schizophrenia disorders: perspectives from the spectrum. American Journal of Psychiatry, 161, 398-413.

Silver, H., Feldman, P., Bilker, W., Gur, R.C. (2003). Working memory deficit as a core neuropsychological dysfunction in Schizophrenia. American Journal of Psychiatry, 160(10), 1809-16.

Simon, T.J., Ding, L., Bish, J.P., McDonald-McGinn, D.M., Zackai, E.H., Gee, J. (2005). Volumetric, connective, and morphologic changes in the brains of children with chromosome 22q11.2 deletion syndrome: an integrative study. NeuroImage, 25(1), 169-180.

Simon, A.E., Dvorsky, D.N., Boesch, J., Roth, B., Isler, E., Schueler, P., Petralli, C., Umbricht, D. (2006). Defining Subjects at Risk for Psychosis: A Comparison of Two Approaches. Schizophrenia Research, 81, 83-90.

Snitz, B.E., Macdonald, A.W. 3rd, Carter, C.S. (2006). Cognitive deficits in unaffected first-degree relatives of Schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophrenia Bulletin, 32(1), 179-94.

Sobin, C., Kiley-Brabeck, K., Karayiorgou, M. (2005). Lower prepulse inhibition in children with the 22q11 deletion syndrome. American Journal of Psychiatry, 162, 1090-1099.

Sobin, C., Monk, S.H., Kiley-Brabeck, K., Khuri, J., Karayiorgou, M.V.(2006). Neuromotor deficits in children with the 22q11 deletion syndrome. Movement Disorders, 21(12), 2082-2089.

Swillen, A., Devriendt, K., Legius, E., Eyskens, B., Dumoulin, M., Gewillig, M., Fryns, J.P. (1997). Intelligence and psychosocial adjustment in velo-cardio-facial syndrome: a study of 37 children and adolescents with VCFS. Journal of Medical Genetics, 34, 453-458.

Swillen, A., Devriendt, K., Legius, E., Prinzie, P., Vogels, A., Ghesquiete, P., Fryns, J.P. (1999). Genetic Counseling, 10(1), 79-88.

Swillen, A., Feyes, H., Adraens, T., Nelissen, L., Mertens, L., Gewillig, M., Devriendt, K., Fryns, J.P. (2005). Early motor development in young children with 22q.11 deletion syndrome and a conotruncal heart defect. Developmental Medicine & Child Neurology, 47, 797-802.

Torrey, E.F. (1987). Prevalence studies in Schizophrenia. *British Journal of Psychiatry*, 150, 598-608.

Trestman, R.L., Keefe, R.S.E., Mitropoulou, V., Harvey, P.D., deVegvar, M.L., Lees-Roitman, S., Davidson, M., Aronson, A., Silverman, J., Siever, L.J. (1995). Cognitive function and biological correlates of cognitive performance in schizotypal personality disorder. Psychiatry Research, 59, 127-136.

Trotman, H., McMillan, A., Walker, E. (2006). Cognitive function and symptoms in adolescents with schizotypal personality disorder. Schizophrenia Bulletin, 32(3), 489-497.

Van Aken, K., De Smedt, B., Van Roie, A., Gewillig, M., Devriendt, K., Fryns, J.P., Simons, J., Swillen, A. (2007). Motor develop ment in school-aged children with 22q11 deletion (velocardiofacial/DiGeorge syndrome). Developmental Medicine & Child Neurology, 49(3), 210-213.

Van Amelsvoort, T., Daly, E., Henry, J., Robertson, D., Ng, V., Owen, M., Murphy, K.C., Murphy, D.G.M. (2004a). Brain anatomy in adults with velocardiofacial syndrome with and without Schizophrenia: preliminary results of a structured magnetic resonance imaging study. Archives of General Psychiatry, 61, 1085-1096.

Van Amelsvoort, T., Henry, J., Morris, R., Owen, M., Linszen, D., Murphy, K., Muphy, D. (2004b). Cognitive deficits associated with Schizophrenia in velo-cardio-facial syndrome. Schizophrenia Research, 70, 223-232.

Van Os, J., Linscott, R.J., Myin-Germeys, I., Delespaul, P., Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychological Medicine, 39, 179-195.

Voglmaier, M.M., Seidman, L.J., Niznikiewicz, M.A., Dickey, C.C., Shenton, M.E., McCarley, R.W. (2000). Verbal and nonverbal neuropsychological test performance in subjects with schizotypal personality disorder. American Journal of Psychiatry, 157, 787-793.

Voglmaier, M.M., Seidman, L.J., Niznikiewicz, M.A., Dickey, C.C., Shenton, M.E., McCarley, R.W. (2005). A comparative profile analysis of neuropsychological

function in men and women with schizotypal personality disorder. Schizophrenia Research, 74, 43-49.

Walker E, Lewine RJ, 1990. Prediction of Adult-Onset Schizophrenia From Childhood Home Movies of the Patients. Am J Psychiatry, 147, 1052-56.

Walker, E.F., Savoie, T., Davis, D. (1994). Neuromotor precursors of Schizophrenia. *Schizophrenia Bulletin*, 20(3), 441-451.

Webb, C.T., Levinson, D.F. (1993). Schizotypal and paranoid personality disorder in the relatives of patients with Schizophrenia and affective disorders: a review. Schizophrenia Research, 11(1), 81-92.

Weinberger, D.R., Torrey, E.F., Neophytides, A.N., Wyatt, R.J. (1979). Structural abnormalities in the cerebral cortex of chronic schizophrenic patients. Arch Gen Psychiatry, 36(9), 935-939.

Weiser, M., Noy, S., Kaplan, Z., Reichenberg, A., Yazvitsky, R., Nahon, D., Grotto, I., Knobler, H.Y. (2003). Generalized cognitive impairment in male adolescents with schizotypal personality disorder. American Journal of Medical Genetics Part B (Neuropsychiatric Genetics), 116B, 36-40.

Welham, J., Scott, J., Williams, G., Najman, J., Bor, W., O'Callaghan, M., McGrath, J. (2008). Emotional and behavioral antecedents of young adults who screen positive for non-affective psychosis: a 21-year birth cohort study. Psychological Medicine, 8, 1-10.

Williams, N.M., Owen, M.J. (2004). Genetic abnormalities of chromosome 22 and the development of psychosis. *Current Psychiatry Reports*, 6(3), 176-182.

Woods, S.W., Addington, J., Cadenhead, K.S., Cannot, T.D., Cornblatt, B.A., Heinssen, R., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Walker, E.F., McGlashan, T.H. (2009). Validity of the prodromal risk syndrome for first psychosis: Findings from the north American prodrome longitudinal study. Schizophrenia Bulletin. *In Press.*

Witthaus, H., Brüne, M., Kaufmann, C., Bohner, G., Ozgürdal, S., Gudlowski, Y., Heinz, A., Klingebiel, R., Juckel, G. (2008). White matter abnormalities in subjects at ultra high-risk for Schizophrenia and first-episode schizophrenic patients. Schizophrenia Research, 102(1-3), 141-149.

Yung, A.R., Phillips, L.J., Pan Yuen, H., Francey, S.M., McFarlane, C.A., Hallgren, M., McGorry, P.D. (2003). Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophrenia Research, 60(1), 21-32.

Zinkstok, J., van, Amelsvoort, T. (2005). Neuropsychological profile and neuroimaging in patients with 22q11.2 deletion syndrome: a review. Child Neuropsychology, 11, 21-37.

Table 1

Demographic Characteristics by Diagnostic Group and Measure

	SIPS			CBCL		
	Controls	**SPD**	**22q11DS**	**Controls**	**SPD**	**22q11DS**
Age[1]	15.9(.503)	16.33(2.25)	19.19(4.154)	15.69(2.24)	15.59(1.943)	15(2.32)
Gender						
Male	28	25	14	28	25	8
Female	23	14	18	23	14	6
Race/Ethnicity						
African American	24	8	5	24	8	2
Hispanic	0	1	2	0	1	1
Caucasian	26	28	24	26	28	11
Asian	0	1	1	0	1	0
Mixed Race or other	1	1	0	1	1	0

[1] Value (SD)

Table 1: Total number of participants from whom data were collected, parsed by gender and race/ethnicity. This larger sample was used for the covariance analyses. Ages did not differ between groups for the CBCL, but the 22q11DS group was significantly older than the other two groups on the SIPS.

Table 2

Demographic Characteristics of Age, Sex, and Ethnicity Matched Diagnostic Groups

	SIPS			CBCL		
	Controls	**SPD**	**22q11DS**	**Controls**	**SPD**	**22q11DS**
Age[1]	17 (1.70)	17.17 (2.02)	17.48 (2.50)	15.69 (1.03)	15.62 (1.12)	15.54 (1.20)
Gender						
Male	11	11	11	7	7	7
Female	12	12	12	6	6	6
Race/Ethnicity						
African American	9	4	3	4	2	2
Hispanic	0	1	2	0	1	1
Caucasian	13	18	17	9	10	10
Asian	0	0	1	0	0	0
Mixed Race or other	1	0	0	0	0	0

[1] Value (SD)

Table 2: Age and gender were optimally matched, as was ethnicity, where possible. In order to match optimally, 4 control, 4 SPD, and 1 22q11DS individuals were unique to the CBCL analyses and 14 controls, 14 SPD, 11 22q11DS individuals were unique to the SIPS analyses.

Table 3

Correlations etween Covariates and Dependant Variables By Diagnostic Group

CBCL					SIPS			
		Age	Gender	Ethnicity		Age	Gender	Ethnicity
anxious/depressed		-0.131	-0.098	-0.187				
	Control	-0.119	-0.098	-0.04	*Positive Symptoms*	0.107	**-0.181**	-0.114
	SPD	-0.208	-0.036	-0.021	Control	0.187	**-0.286**	-0.035
	22q11DS	-0.105	0.163	-0.178	SPD	-0.266	-0.231	-0.012
withdrawn/depressed		-0.081	-0.178	-0.133	22q11DS	0.215	-0.144	0.127
	Control	-0.124	-0.129	-0.04	*Negative Symptoms*	**0.216**	**-0.222**	-0.061
	SPD	-0.094	-0.167	-0.116	Control	0.08	**-0.347**	0.175
	22q11DS	0.187	-0.126	0.3	SPD	-0.137	**-0.421**	-0.047
somatic complaints		-0.105	-0.016	-0.192	22q11DS	0.141	-0.295	0.088
	Control	-0.126	-0.011	-0.201	*Disorganized Sympton*	**0.192**	**-0.245**	**-0.207**
	SPD	-0.186	-0.055	-0.092	Control	0.033	**-0.309**	-0.17
	22q11DS	0.252	0.236	-0.074	SPD	-0.082	-0.279	-0.1
social problems		-0.128	-0.099	**-0.213**	22q11DS	0.13	**-0.397**	-0.117
	Control	**-0.304**	-0.134	-0.074	*Generalized Symptom*	**0.288**	-0.156	-0.032
	SPD	0.001	-0.145	-0.156	Control	0.104	-0.217	0.191
	22q11DS	0.041	0.144	0.113	SPD	0.096	-0.205	-0.09
thought problems		**-0.218**	-0.181	-0.154	22q11DS	0.246	-0.302	0.258
	Control	-0.209	-0.266	-0.131				
	SPD	**-0.33**	0.038	-0.069				
	22q11DS	-0.064	-0.359	0.022				
attention problems		-0.09	-0.08	-0.124				
	Control	-0.138	-0.126	-0.184				
	SPD	0.029	0.029	0.102				
	22q11DS	-0.311	0.09	0.235				
delinquency		0.099	-0.125	-0.083				
	Control	0	-0.246	-0.081				
	SPD	0.206	0.1	-0.125				
	22q11DS	0.109	-0.295	0.264				
aggression problems		-0.18	-0.128	-0.156				
	Control	-0.227	**-0.285**	-0.209				
	SPD	-0.156	0.129	0.005				
	22q11DS	-0.197	-0.019	-0.098				
INTERNALIZING PROBLEMS		-0.144	-0.157	**-0.203**				
	Control	-0.218	-0.188	-0.178				
	SPD	-0.106	-0.143	-0.058				
	22q11DS	0.076	0	0.167				
EXTERNALIZING PROBLEMS		-0.093	-0.159	-0.159				
	Control	-0.155	**-0.312**	-0.245				
	SPD	-0.003	0.114	-0.049				
	22q11DS	-0.182	-0.197	0.253				

Table 3: Significant correlations between covariates and dependant variables are listed in bold print. The magnitude and, in some cases, direction of effects often differ by diagnostic group. Gender was coded as -1 for males and 1 for females. Ethnicity was coded as 1 for Caucasian, 2 for African American, 3 as Hispanic, and 5 for Asian.

Table 4

Partial R^2 and Significance for SIPS Diagnostic Group Contrasts

		No Covariates		Age		Ethnicity		Gender		All 3 Covariates	
		R^2	p	R^2	p	R^2	p	R^2	p	R^2	p
Positive Symptoms n=122	HR v. Control	.386	**>.001**	.371	**>.001**	.369	**>.001**	.375	G **>.001**	.355	G **>.001**
	SPD v. 22q		**.007**		**.009**		**.008**		**.019**		**.021**
Negative Symptoms n=121	HR v. Control	.333	**>.001**	.328	A **>.001**	.317	**>.001**	.340	G **>.001**	.283	AG **>.001**
	SPD v. 22q		.091		.143		.083		**.031**		**.054**
Disorganized Symptoms n=121	HR v. Control	.410	**>.001**	.281	A **>.001**	.344	E **>.001**	.407	G **>.001**	.319	AG **>.001**
	SPD v. 22q		.715		.619		.680		.912		.848
General Symptoms n=121	HR v. Control	.305	**>.001**	.235	A **>.001**	.265	**>.001**	.308	**>.001**	.212	AG **>.001**
	SPD v. 22q		.335		.772		.347		.202		.588
22q11DS age outliers removed*											
Positive Symptoms n=114	HR v. Control	.414	**>.001**	.412	**>.001**	.055	E **>.001**	.399	G **>.001**	.397	G **>.001**
	SPD v. 22q		**.002**		**.003**		**.002**		**.004**		**.006**
Negative Symptoms n=113	HR v. Control	.314	**>.001**	.303	**>.001**	.009	E **>.001**	.312	G **>.001**	.303	G **>.001**
	SPD v. 22q		.229		.217		.223		.125		.109
Disorganized Symptoms n=113	HR v. Control	.425	**>.001**	.409	**>.001**	.002	E **>.001**	.413	G **>.001**	.350	G **>.001**
	SPD v. 22q		.508		.514		.498		.764		.717
General Symptoms n=113	HR v. Control	.292	**>.001**	.264	(.058) **>.001**	.000	E **>.001**	.287	(.086) **>.001**	.242	G (A .058) **>.001**
	SPD v. 22q		.901		.957		.894		.732		.865

*Participants older than 21 dropped from the 22q11DS group

Table 4: Values listed are after all regression blocks are accounted for. R^2 values represent the proportion of variance in dependant variables accounted for by both diagnostic group contrasts, together. p values represent the significance of each contrast, by itself—significant values are listed in bold print. Where demographic variables were significant in a model, they are listed with an E for ethnicity, G for gender, or A for age. Marginally significant covariates have p values listed in parentheses.

Table 5

SIPS: Observed Power and Required Sample Sizes for Adequately Powered Diagnostic Group Contrasts

	No Covariates			Age			Ethnicity			Gender			All Covariates		
	R^2	r	power	R^2	r	power	R^2	r	power	R^2	r	power	R^2	r	power
Positive Sx															
SPD v. 22q	0.055	**0.235**	0.645 108	0.081	**0.285**	0.798	0.056	0.237	0.652 106	0.042	0.205	0.541 143	0.067	**0.259**	0.723 88
control v. clinical	0.331	**0.575**	1.000	0.290	**0.539**	1.000	0.312	0.559	1.000	0.333	**0.577**	1.000	0.288	**0.537**	1.000
Negative Sx															
SPD v. 22q	0.007	0.084	0.173 872	0.000	0.000	0.050	0.006	0.077	0.159 1038	0.014	**0.118**	0.257 440	0.002	**0.045**	0.102 3049
control v. clinical	0.325	**0.570**	1.000	0.281	**0.530**	1.000	0.310	**0.557**	1.000	0.326	**0.571**	1.000	0.281	**0.530**	1.000
Disorganized Sx															
SPD v. 22q	0.005	0.071	0.147 1222	0.021	0.145	0.336 290	0.007	0.084	0.173 872	0.002	0.045	0.102 3049	0.015	0.122	0.268 411
control v. clinical	0.405	**0.636**	1.000	0.348	**0.590**	1.000	0.337	**0.581**	1.000	0.405	**0.636**	1.000	0.304	**0.551**	1.000
General Sx															
SPD v. 22q	0.001	0.032	0.084 6033	0.004	0.063	0.132 1553	0.001	0.032	0.084 6033	0.003	0.055	0.118 2039	0.002	0.045	0.102 3049
control v. clinical	0.304	**0.551**	1.000	0.231	**0.481**	0.999	0.264	**0.514**	1.000	0.304	**0.551**	1.000	0.209	**0.457**	0.999
22q11DS age outliers removed*															
Positive Sx															
SPD v. 22q	0.107	**0.327**	0.858	0.109	**0.330**	0.864	0.103	**0.321**	0.845	0.092	**0.303**	0.803	0.094	**0.307**	0.812
control v. clinical	0.307	**0.554**	1.000	0.303	**0.550**	1.000	0.298	**0.546**	1.000	0.307	**0.554**	1.000	0.303	**0.550**	1.000
Negative Sx															
SPD v. 22q	0.000	0.000	0.050	0.000	0.000	0.050	0.000	0.000	0.050	0.000	0.000	0.050	0.000	0.000	0.050
control v. clinical	0.314	**0.560**	1.000	0.302	**0.550**	1.000	0.305	**0.552**	1.000	0.311	**0.558**	1.000	0.303	**0.550**	1.000
Disorganized Sx															
SPD v. 22q	0.026	0.161	0.358 234	0.031	0.176	0.405 195	0.024	0.155	0.400 253	0.018	0.134	0.280 340	0.021	0.145	0.310 290
control v. clinical	0.399	**0.632**	1.000	0.378	**0.615**	1.000	0.338	**0.581**	1.000	0.395	**0.628**	1.000	0.329	**0.574**	1.000
General Sx															
SPD v. 22q	0.007	0.084	0.163 872	0.012	0.110	0.219 507	0.007	0.084	0.163 872	0.004	0.063	0.125 1553	0.008	0.089	0.173 776
control v. clinical	.284	**0.533**	1.00	0.25	**0.503**	1.00	0.26	**0.508**	1.00	0.28	**0.532**	1.00	0.23	**0.484**	1.00

*Participants older than 21 dropped from the 22q11DS group
significant r value at p =.05 denoted in bold print

Table 5: r and R^2 values are listed for each individual contrast, as it was entered in the model; SPD v. 22q contrasts were entered first. Where observed power was below 80%, the total sample size required to yield p=.05 with the same effect size is listed under the observed power. The larger sample includes 51 controls, 39 individuals with SPD, and 32 individuals with 22q11DS. The smaller sample includes only 24 individuals with 22q11DS.

Table 6

Mean CBCL Scores: Age-Matched

	Controls	SPD	22q11DS
anxious/depressed			
Mean *†	53.846	73.615	59.692
SD	8.395	11.594	7.867
withdrawn/depressed			
Mean †	56.769	68	63.846
SD	9.462	10.288	9.388
somatic complaints			
Mean	55.538	62.385	59.231
SD	7.230	12.894	7.373
social problems			
Mean †‡	53.077	70.077	63.308
SD	6.726	9.340	7.532
thought problems			
Mean *†	57.385	70.615	61.538
SD	9.023	11.207	6.463
attention problems			
Mean *†	55.538	67.538	59.615
SD	6.333	9.863	6.850
delinquency			
Mean	55.154	60.692	54.385
SD	6.817	8.087	6.935
aggression			
Mean	55.692	63.923	55
SD	10.664	8.411	8.935
INTERNALIZING PROBLEMS			
Mean †‡	48.769	70.846	61.846
SD	14.137	9.814	8.523
EXTERNALIZING PROBLEMS			
Mean *†	50.538	62.538	49.769
SD	12.732	8.762	12.139

** Significant difference between SPD and 22q11DS groups at p <.01*

† Significant difference between control and SPD groups at p <.01

‡ Significant difference betwee n control and 22q11DS groups at p <.01

Table 6: Means and Standard Deviations are listed for CBCL scores in the demographic-matching analyses. With the exception of externalizing problems (including the delinquency and aggression subscales) 22q11DS scores are intermediate to those of the control and SPD groups.

Table 7

Partial R^2 and Significance for CBCL Diagnostic Group Contrasts

	No Covariates		Age		Ethnicity		Gender		All 3 Covariates	
	R^2	p	R^2	p	R^2	p	R^2	p	R^2	p
Anxious/Depressed	.302		.301		.226	E	.296		.229	E
HR v. Control		**>.001**		**>.001**		**.001**		**>.001**		**.001**
SPD v. 22q		**.002**		**.001**		**.001**		**.002**		**.001**
Withdrawn	.183		.180		.120	E	.174		.119	E
HR v. Control		**>.001**		**>.001**		**0.001**		**>.001**		**.001**
SPD v. 22q		.486		.453		.450		.523		.456
Somatic Complaints	.099		.098		.063	E	.099		.065	E
HR v. Control		**.018**		**.024**		.102		**.019**		.118
SPD v. 22q		.190		.162		.158		.191		.131
Social Problems	.258		.255		.178	E	.251		.178	E
HR v. Control		**>.001**		**>.001**		**>.001**		**>.001**		**>.001**
SPD v. 22q		.067		**.052**		**.049**		.073		**.041**
Thought Problems	.202		.200	A	.185		.194		.185	A
HR v. Control		**.001**		**.001**		**.001**		**.001**		**.002**
SPD v. 22q		**.034**		**.018**		**.033**		**.038**		**.021**
Attention Problems	.144		.144		.097	E	.143		.100	E
HR v. Control		**.012**		**.016**		.084		**.013**		.097
SPD v. 22q		**.035**		**.029**		**.024**		**.036**		**.019**
Delinquency	.061		.058		.059		.059		.053	
HR v. Control		.804		.862		.432		.781		.471
SPD v. 22q		**.015**		**.019**		**.012**		**.016**		**.017**
Aggression	.067		.072		.055	E	.063		.060	
HR v. Control		.603		.725		.844		.642		.767
SPD v. 22q		**.024**		**.014**		**.018**		**.027**		**.012**
INTERNALIZING	.294		.289		.189	E	.283		.189	E
HR v. Control		**>.001**		**>.001**		**>.001**		**>.001**		**>.001**
SPD v. 22q		.122		.093		.081		.136		.070
EXTERNALIZING	.080		.083		.065	E	.074		.065	E
HR v. Control		.550		.617		.671		.607		.649
SPD v. 22q		**.013**		**.011**		**.007**		**.016**		**.007**

n=104 for all cells

Table 7: Values listed are after all regression blocks are accounted for. R^2 values represent the proportion of variance in dependant variables accounted for by both diagnostic group contrasts, together. P values represent the significance of each contrast, by itself—significant values are listed in bold print. Where demographic variables were significant, they are listed with an E for ethnicity, G for gender, or A for age. Marginally significant covariates have p values listed in parentheses.

Table 8

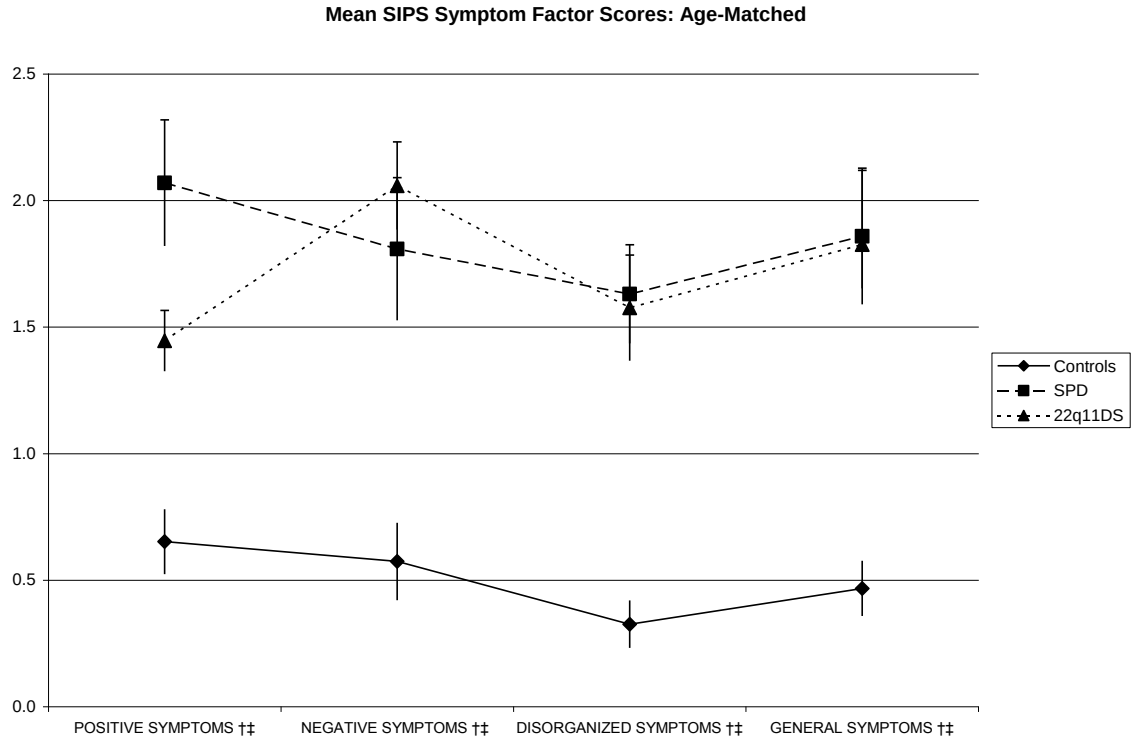
CBCL: Observed Power and Required Sample Sizes for Adequately Powered Diagnostic Group Contrasts

	No Covariates			Age			Ethnicity			Gender			All Covariates		
	R^2	r	power	R^2	r	power	R^2	r	power	R^2	r	power	R^2	r	power
Anxious/Depressed															
SPD v. 22q	0.173	**0.416**	0.950	0.180	**0.424**	0.957	0.150	**0.387**	0.915	0.169	**0.411**	0.944	0.157	**0.396**	0.927
clinical v. control	0.129	**0.359**	0.988	0.120	**0.346**	0.982	0.076	**0.276**	0.897	0.127	**0.356**	0.987	0.072	**0.268**	0.880
Withdrawn															
SPD v. 22q	0.043	**0.207**	0.450	0.045	**0.212**	0.466	0.032	**0.179**	0.368	0.039	**0.197**	0.420	0.032	**0.179**	0.368
			140			133			189			155			189
clinical v. control	0.140	**0.374**	0.993	0.135	**0.367**	0.991	0.088	**0.297**	0.934	0.135	**0.367**	0.991	0.087	**0.295**	0.931
Somatic Complaints															
SPD v. 22q	0.048	**0.219**	0.487	0.051	**0.226**	0.509	0.039	**0.197**	0.420	0.047	**0.217**	0.481	0.043	**0.207**	0.450
			125			117			155			127			140
clinical v. control	0.051	**0.226**	0.760	0.047	**0.217**	0.728	0.024	0.155	0.478	0.051	**0.226**	0.760	0.022	0.148	0.449
Social Problems			117			127			253			117			278
SPD v. 22q	0.101	**0.318**	0.778	0.106	**0.326**	0.797	0.084	**0.290**	0.703	0.097	**0.311**	0.760	0.088	**0.297**	0.722
			57						69			117			66
clinical v. control	0.157	**0.396**	0.997	0.148	**0.385**	0.995	0.094	**0.307**	0.948	0.154	**0.392**	0.996	0.091	**0.302**	0.941
Thought Problems															
SPD v. 22q	0.104	**0.322**	0.788	0.113	**0.336**	0.821	0.099	**0.315**	0.770	0.098	**0.313**	0.765	0.105	**0.324**	0.792
			55						58			59			55
clinical v. control	0.099	**0.315**	0.957	0.087	**0.295**	0.931	0.086	**0.293**	0.928	0.095	**0.308**	0.949	0.080	**0.283**	0.911
Attention Problems															
SPD v. 22q	0.089	**0.298**	0.725	0.093	**0.305**	0.744	0.073	**0.270**	0.644	0.088	**0.297**	0.722	0.078	**0.279**	0.671
			65			62			81			66			75
clinical v. control	0.055	**0.235**	0.789	0.051	**0.226**	0.760	0.024	0.155	0.478	0.055	**0.235**	0.789	0.022	0.148	0.449
Delinquency			108			117			153			108			278
SPD v. 22q	0.060	**0.245**	0.568	0.058	**0.241**	0.555	0.053	**0.230**	0.521	0.058	**0.241**	0.555	0.049	**0.221**	0.493
			99			102			113			102			122
clinical v. control	0.001	0.032	0.093	0.000	0.000	0.050	0.006	0.077	0.194	0.001	0.032	0.093	0.005	0.071	0.178
Aggression			6033						1038			6033			1222
SPD v. 22q	0.065	**0.255**	0.599	0.071	**0.266**	0.632	0.055	**0.235**	0.537	0.061	**0.247**	0.574	0.059	**0.243**	0.561
			91			83			108			97			100
clinical v. control	0.003	0.055	0.139	0.001	0.032	0.093	0.000	0.000	0.050	0.002	0.045	0.117	0.001	0.032	0.093
Internalizing			2039			6033						3049			6033
SPD v. 22q	0.094	**0.307**	0.749	0.100	**0.316**	0.773	0.075	**0.274**	0.656	0.088	**0.297**	0.722	0.078	**0.279**	0.671
			61			58			78			66			75
clinical v. control	0.200	**0.447**	1.000	0.189	**0.435**	0.999	0.115	**0.339**	0.978	0.195	**0.442**	1.000	0.111	**0.333**	0.973
Externalizing															
SPD v. 22q	0.077	**0.277**	0.665	0.081	**0.285**	0.688	0.064	**0.253**	0.592	0.071	**0.266**	0.632	0.063	**0.251**	0.586
			76			72			92			83			94
clinical v. control	0.003	**0.055**	0.139	0.002	0.045	0.117	0.002	0.045	0.117	0.002	0.045	0.117	0.002	0.045	0.117
			2039			3049			3049			3049			3049

n=39, 14, and 51 for SPD 22q11DS, and controls, respectively
significant r value at p =.05 denoted in bold print
* = total n required for power of 80%

Table 8: r and R^2 values are listed for each individual contrast, as it was entered in the model; SPD v. 22q contrasts were entered first. Where observed power was below 80%, the total sample size required to yield p=.05 with the same effect size is listed under the observed power.

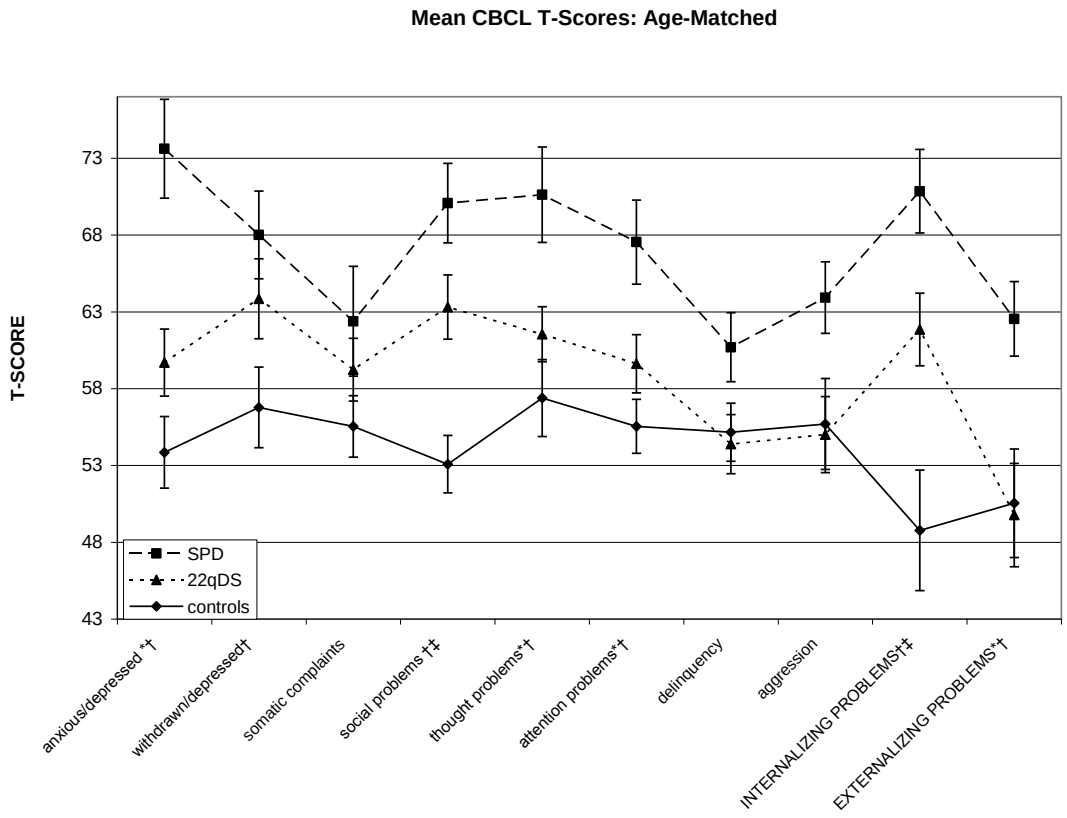
Figure 1



** Significant difference between SPD and 22q11DS groups at p <.01*
† Significant difference between control and SPD groups at p <.01
‡ Significant difference betwee n control and 22q11DS groups at p <.01

Figure 1: Error bars represent ±1 standard error of the mean. Clinical groups had significantly higher scores than controls on all subscales, but did not differ from each other in the demographic matching analyses. However, in the covariance analyses, the SPD group had higher positive symptom scores and a trend toward lower negative symptom scores than the 22q11DS group.

Figure 2



** Significant difference between SPD and 22q11DS groups at p <.01*
† Significant difference between control and SPD groups at p <.01
‡ Significant difference betwee n control and 22q11DS groups at p <.01

Figure 2: CBCL scores are graphed by diagnostic group, with error bars denoting ±1 standard error of the mean.

Figure 3

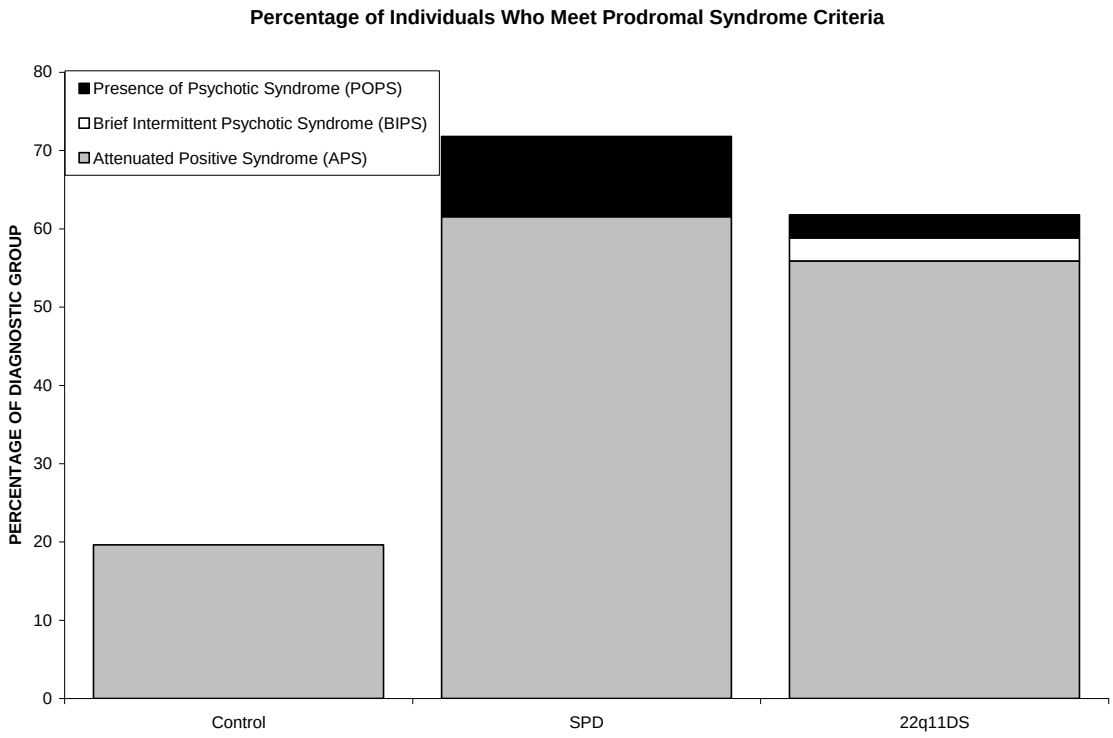


Figure 3: Proportions of each group that meet criteria for the APS and BIPS prodromal syndromes are shown, as are proportions that meet for POPS. The two clinical groups have approximately the same proportions of participants that meet symptom severity (but not duration) criteria for a prodromal syndrome.

Appendix 1

Mean SIPS Scores by Diagnostic Group: Age-Matched

	Controls			SPD			22q11DS		
	Mean	**SD**	**SEM**	**Mean**	**SD**	**SEM**	**Mean**	**SD**	**SEM**
POSITIVE SYMPTOMS	0.652	0.616	0.128	2.070	1.193	0.249	1.446	0.577	0.120
delusional ideas	0.652	0.982	0.205	2.435	1.879	0.392	1.478	0.665	0.139
persecutory ideas	0.652	1.027	0.214	2.348	1.695	0.353	1.652	1.152	0.240
grandiosity	0.739	0.915	0.191	1.304	1.428	0.298	0.739	1.096	0.229
perceptual abnormalities	0.696	0.926	0.193	2.435	1.830	0.382	1.783	1.204	0.251
disorganized communication	0.609	0.891	0.186	2.000	1.537	0.321	1.478	1.123	0.234
NEGATIVE SYMPTOMS	0.574	0.735	0.153	1.808	1.352	0.282	2.058	0.830	0.173
social anhedonia	0.826	1.370	0.286	2.826	2.059	0.429	3.000	1.651	0.344
avolition	0.609	1.340	0.279	1.913	1.730	0.361	1.957	1.522	0.317
impaired expression of emotion	0.826	1.114	0.232	1.696	1.941	0.405	1.696	1.550	0.323
unusual experience of emotion/self	0.391	0.722	0.151	1.000	1.537	0.321	1.043	1.186	0.247
problems with ideational richness	0.130	0.344	0.072	1.348	1.229	0.256	2.913	1.676	0.350
role functioning difficulties	0.609	1.373	0.286	1.826	1.946	0.406	1.913	1.443	0.301
DISORGANIZED SYMPTOMS	0.326	0.449	0.094	1.630	0.935	0.195	1.576	1.001	0.209
odd behavior/appearance	0.130	0.344	0.072	1.696	1.608	0.335	1.435	1.273	0.265
bizarre thinking	0.174	0.650	0.136	1.174	1.193	0.249	0.783	1.043	0.217
problems with attention/focus	0.826	1.267	0.264	2.304	1.396	0.291	2.652	0.935	0.195
problems with hygiene	0.174	0.491	0.102	1.391	1.500	0.313	1.304	1.608	0.335
GENERAL SYMPTOMS	0.467	0.524	0.109	1.859	1.290	0.269	1.826	0.831	0.173
sleep disturbance	1.043	1.331	0.277	2.391	1.751	0.365	1.609	1.406	0.293
dysphoric mood	0.565	0.896	0.187	2.696	2.204	0.460	2.391	1.500	0.313
motor disturbance	0.087	0.417	0.087	0.696	1.490	0.311	1.826	1.557	0.325
impaired stress tolerance	0.174	0.388	0.081	1.696	2.077	0.433	1.478	1.201	0.250

Appendix 1: Mean SIPS item scores are listed by diagnostic group. Across all groups, only social anhedonia in the 22q11DS group had an average score in the prodromal range (3-5). Scores of 0-6 correspond with ratings of "absent," "questionably present," "mild," "moderate," "moderately severe," "severe but not psychotic," and "severe and psychotic," respectively.

Appendix 2

Skewness Values by Diagnostic Group

CBCL		SIPS	
anxious/depressed	1.096	*Positive Symptoms*	0.788
Control	1.974	0.904	
SPD	0.359	-0.171	
22q11DS	0.335	1.679	
withdrawn/depressed	1.125	*Negative Symptoms*	0.741
Control	1.573	1.397	
SPD	0.669	0.64	
22q11DS	0.969	0.77	
somatic complaints	1.006	*Disorganized Symptoms*	0.664
Control	1.588	1.029	
SPD	0.502	-0.363	
22q11DS	0.175	0.639	
social problems	0.677	*General Symptoms*	0.916
Control	1.326	1.143	
SPD	0.043	0.778	
22q11DS	0.114	0.499	
thought problems	0.663		
Control	1.113		
SPD	0.366		
22q11DS	-0.361		
attention problems	0.945		
Control	1.635		
SPD	0.593		
22q11DS	0.213		
delinquency	0.918		
Control	1.263		
SPD	0.386		
22q11DS	1.781		
aggression problems	0.87		
Control	1.344		
SPD	0.194		
22q11DS	1.687		
INTERNALIZING PROBLEMS	-0.047		
Control	0.354		
SPD	-0.337		
22q11DS	-0.839		
EXTERNALIZING PROBLEMS	-0.135		
Control	0.207		
SPD	-0.899		
22q11DS	0.499		

Appendix 2: Skewness values suggest that the distributions of SIPS and CBCL scores differ by diagnostic group.