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The relationship between prodromal symptoms and autistic features: A comparison of schizotypal personality disorder and 22q11.2 deletion syndrome

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Abstract

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By Michelle L. Esterberg

Despite clear diagnostic distinctions, schizophrenia and autism share symptoms on several dimensions. Recent research has suggested the two disorders overlap in etiology, particularly with respect to genetics. Studying the relationship between psychotic-like and autistic-like symptoms in risk groups such as 22qDS and schizotypal personality disorder has the potential to shed light on etiologic factors; thus, the current study examined prodromal symptoms and autistic features in a sample of 22qDS and SPD subjects using standardized measures (SIPS and ADI-R). Results showed that SPD subjects showed significantly more severe social and stereotypic autistic features, as well as more severe positive prodromal symptoms. The two groups did not differ on negative, disorganized, or general prodromal symptoms, but were distinguishable based on correlations between prodromal and autistic features. Furthermore, cluster and discriminant function analyses revealed empirically-derived groups based on autistic and prodromal symptom severity. Finally, analyses showed that genotype of COMT, a risk gene located in the 22q deletion region, interacted with diagnostic group to influence severity of prodromal symptoms. Results herein highlight the importance of studying overlap in diagnostic phenomenology in groups at risk for developing either psychosis or autism, and point to a potential chromosomal region that confers risk for neurodevelopmental disorders such as schizophrenia and autism.

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Autistic disorder (AD) and schizophrenia are considered two of the most debilitating psychiatric disorders. Current diagnostic taxonomies distinguish them on the basis of both symptoms and age at onset, and they are presumed to have different etiologies. But early conceptualizations of child psychiatric disorders assumed that these two disorders had a common etiology. Eminent figures in psychiatry, such as Lauretta Bender (1947), argued that what we currently call autism was essentially an early-onset and more severe form of schizophrenia.

Over the years, the diagnostic boundaries between AD and schizophrenia have been made more explicit. Nonetheless, the breadth of the two classes has broadened, so that it is now assumed that there is a spectrum of autistic and schizophrenic disorders. Included in the autistic spectrum is Asperger's disorder, a disorder that involves milder versions of some of the symptoms of autism. Similarly, the hypothesized spectrum of schizophrenia disorders includes milder syndromes, such as schizotypal personality disorder (SPD). While there are explicit guidelines for differential diagnoses for AD and schizophrenia, there is considerable overlap in the disorders that are considered to be on the mild end of the spectrums. For example, both Asperger's disorder and SPD involve social deficits and odd behaviors, as well as difficulties with emotional functioning. Moreover, some motor symptoms, such as stereotypies, are observed in both autistic-spectrum and schizophrenia-spectrum disorders.

Schizotypal personality disorder has been the focus of more intensive investigation in recent years because it has been shown to be both genetically and developmentally linked with schizophrenia. Individuals who are diagnosed with schizophrenia in adulthood often manifest SPD in adolescence, prior to the clinical onset of schizophrenia. Furthermore, like schizophrenia, SPD is associated with childhood behavioral problems, including higher rates of internalizing problems, as well as difficulties in cognitive functioning. Individuals with SPD also show similarities in the functioning of several biological vulnerability markers relative to individuals with schizophrenia. Therefore, SPD as a risk factor for schizophrenia has become a focus of researchers interested in investigating the development of psychosis. Interestingly, there is

evidence that adolescents who meet criteria for SPD also manifest an elevated rate of autistic-like behaviors (ALB), both currently and earlier in childhood (Esterberg, Trotman, Brasfield, Compton, & Walker, 2008).

There has been increased focus on the 22q11.2 deletion syndrome (22qDS), a genetic disorder that shows variable psychiatric phenotypes, including an increased risk for both autistic- and schizophrenia-spectrum disorders (Antshel et al., 2007; Gothelf et al., 2007). This deletion syndrome is a genetic disorder that results in physical abnormalities such as cleft palate, as well as congenital heart defects (Vantrappen et al., 1999). Moreover, approximately 30% of these individuals also develop schizophrenia, with up to half experiencing more broadly defined psychotic disorders at some point in their lives. In childhood, up to 45% manifest autistic features (Antshel et al., 2007; Vorstman et al., 2006). Given that 22qDS is a genetic risk factor for the development of psychosis, researchers have hypothesized that 22qDS can serve as a model for examining the trajectory from genes and chromosomal defects to schizophrenia (Gothelf, Schaer, & Eliez, 2008). Therefore, much like SPD, 22qDS has also become a focus of the investigation of the development of schizophrenia.

Given the associations of both SPD and 22qDS with autistic- and schizophrenia-spectrum symptoms, comparing these two disorders with respect to the presence and severity of ALB might provide insight into developmental similarities and differences between the two diagnostic groups. As noted, research has demonstrated that individuals with SPD show more severe autistic behaviors compared to normal individuals (Esterberg et al., 2008). It has also been shown that schizotypal features are associated with features of Asperger's disorder in non-clinical individuals (Hurst, Nelson-Gray, Mitchell, & Kwapil, 2007). However, to date, there have been no studies comparing autistic- and schizophrenia-spectrum symptoms in both SPD and 22qDS. Such research could lead to greater understanding of the phenomenologic overlap between AD and schizophrenia, and help elucidate common etiologic pathways.

The primary focus of the current study is to extend the findings of Esterberg and colleagues (2008) by examining autistic- and schizophrenic-spectrum symptoms in individuals with 22qDS and adolescents with SPD. Specifically, this study will focus on the measurement of prodromal symptoms, or symptoms that are indicative of risk for psychosis. Furthermore, given that the high prevalence of both ALB and schizophrenia in 22qDS points to potential shared genetic etiologies, as a secondary focus this study also examines these relationships in conjunction with a potential candidate gene. Specifically, the *catechol-O-methyltransferase* (COMT) gene has been implicated in the development of both schizophrenia and AD, and is located in the deletion region of 22qDS; therefore, the relationship between prodromal symptoms and autistic features will be investigated in relation to COMT genotype.

Schizophrenia and Autistic Disorder

First defined Leo Kanner (1943), AD has come to be understood as a neurodevelopmental disorder that is characterized by pervasive developmental abnormalities in social and emotional functioning, as well as behavioral stereotypies, delayed language development, and learning disabilities. Children with AD frequently display repetitive behaviors during play and suffer from a restricted range of interests and activities. According to contemporary criteria, this delay in social development, language, or difficulty with repetitive play must be present before a child is three years old (Tidmarsh & Volkmar, 2003).

Affecting approximately 10 in 10,000 children, AD is classified as a pervasive developmental disorder (PDD) by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Autistic disorder predominately affects males and children with AD frequently suffer from cognitive difficulties as well (Fombonne, 2003a), with some studies indicating that a large percentage of children with AD suffer from mental retardation. Additionally, like many severe psychiatric disorders, longitudinal studies have determined that a diagnosis of autistic disorder is stable, but that functioning in various aspects of life such as school, work, and social relationships varies from individual to individual. Tsatsanis (2003) indicated in a recent review

of outcome literature in autistic disorder that approximately 75% of individuals diagnosed with autistic disorder have a poor outcome.

Schizophrenia is a complex neurodevelopmental disorder that is often chronic, severe, and disabling. Schizophrenia typically has an onset during late adolescence or early adulthood and affects around 1% of the population (Jablensky, 1997). Schizophrenia as an adult-onset disorder is characterized by functioning during premorbid and prodromal time periods, as well as functioning after the onset of psychosis. After the onset of psychosis, an individual with schizophrenia typically suffers from positive symptoms such as delusions and hallucinations, negative symptoms such as a flat affect, alogia, and amotivation, and finally, impaired cognition. Schizophrenia is a disorder that varies greatly in course and outcome, although the majority of people with schizophrenia experience a relatively poor outcome (Jobe & Harrow, 2005).

Historical literature and conceptualizations of AD are informative because they highlight the vast complexities of the disorder. The term "autistic" was first coined by Bleuler in 1911 to describe a cardinal sign of schizophrenia that referred to a withdrawal from the self into a fantasy world (Parnas & Bovet, 1991). According to Bleuler, autism also included impairment in the ability to make social connections with other people, social withdrawal, emotional indifference, behavior rigidity, and an idiosyncratic cognitive style.

In 1943, Leo Kanner published his seminal paper on autism in which he described the case histories of eight boys and three girls who had at some point been diagnosed as "feeble-minded" or as having schizophrenia. In this paper, Kanner described these children as displaying an extreme autistic aloneness and disinterest in others, an inability to relate to oneself, an inability to use language to communicate with others, excellent rote memory, a fear of loud noises and moving objects, repetitious motions and sounds, limitations in spontaneous activity, and an obsessive desire for sameness. With this description, Kanner pointed out that while the experiences of these children resemble the complex presentation of childhood schizophrenia, the

autistic condition differs in many respects from schizophrenia, especially in terms of the age of onset of the two disorders (Kanner, 1943).

While he noted the similarities to schizophrenia, Kanner's distinction was the first to disentangle the term "autistic" from schizophrenia and assign the term to its own classification of disorders. Despite this distinction, researchers for many years continued to believe that autism and schizophrenia were separate representations of the same underlying disorder due to their shared clinical symptoms. Additionally, research during the late 1940's investigated autism as either the earliest manifestation of schizophrenia or as one clinical representation of childhood schizophrenia (Bender, 1947).

Research in the late 1960's and early 1970's subsequently differentiated AD and schizophrenia as two separate disorders, in part due to the work of Rutter (1967) and Kolvin (1971a; 1971b). Kolvin and colleagues (1971a; 1971b) distinguished children with AD from children with schizophrenia by demonstrating that children with schizophrenia usually resemble adults with schizophrenia with respect to symptom presentation and can easily be differentiated from children with AD. Findings from this research group, in combination with other studies (Green et al., 1984; Rutter, 1967) identified several distinct differences between schizophrenia and autistic disorder, including cardinal symptoms, course of disorder, age of onset (earlier in AD), intellectual functioning (lower in AD), gender distribution, pregnancy complications, family history of schizophrenia, and socioeconomic status (lower in schizophrenia).

Despite these distinctions, questions remained about the comorbidity and diagnostic overlap between autistic disorder and schizophrenia. Research attempting to answer these questions has raised conflicting answers. While studies during the 1970's clearly identified the distinctions and differences of the two disorders, other research has indicated the possibility of some children with AD developing schizophrenia later in life. One of the first studies in this area was a case study of a 28-year-old woman who had schizophrenia but also clearly displayed features of AD during her childhood (Darr & Worden, 1951). Subsequent prospective studies

also hinted at the possibility of children with AD later developing schizophrenia as adolescents or adults. Brown (1963) and Reiser and Brown (1964) conducted a follow-up study of children with infantile psychosis, an early phrase used to describe autism, and found that as adolescents, these children displayed some clinical symptoms of schizophrenia.

Similarly, Rutter and colleagues (1967), while noting the differences between AD and schizophrenia in childhood, pointed out that some children with AD displayed odd behavior and seemed to be preoccupied with fantasies when followed up in adolescence. Havelkova (1968) also studied preschool-age children who were diagnosed as psychotic (a term also used to describe AD at that time) and followed these children into adolescence. Results from this follow-up study showed evidence of some of these adolescents receiving diagnoses of schizophrenia. Finally, a paper by Petty and colleagues (1984) presented the case histories of three individuals who met criteria for the diagnosis of AD in early childhood and for schizophrenia in later childhood and adolescence.

However, there were many limitations of these research studies. Of most importance was the lack of delineation between the two disorders prior to the early 1970's. Until this time, it was not clear that AD and schizophrenia represented two distinct disorders that could be distinguished by a number of important factors such as age of onset and clinical presentation. This lack of distinction may have contributed to children who actually met criteria for childhood schizophrenia being classified as having AD, which is a possibility with the sample from Havelkova (1968). As Kolvin (1971a; 1971b) postulated, children with schizophrenia almost always resemble adults with schizophrenia. Those children with childhood schizophrenia would naturally progress into adults with schizophrenia, and therefore could have been mistaken as having AD that progressed into schizophrenia.

Furthermore, the terms "autistic disorder" and "schizophrenia" and "psychosis" were frequently used interchangeably to indicate the same disorder. This lack of stable diagnostic criteria for autistic disorder and schizophrenia and the lack of differentiation between the two

disorders pre-1970 presents a difficulty in interpreting this early research. Additionally, the limited understanding of childhood and adult schizophrenia and the premorbid and prodromal functioning of these two disorders adds more confusion to findings during the 1970's and 1980's. This lack of understanding of the precursors to childhood and adult schizophrenia could have lead to a case of mistaken identity: the premorbid characteristics of schizophrenia mistaken for infantile autism. Because of these limitations, it is still unclear whether children with AD or the features of AD are more likely to develop schizophrenia as adolescents or adults.

There is also a question of comorbidity between autistic disorder and schizophrenia. For example, Bender (1970) conducted a study on the relationship between childhood and adult schizophrenia in a sample of 50 children. The children, who were diagnosed with schizophrenia, were recruited because they also met Kanner's criteria for AD and represented a large group of individuals who met criteria for both disorders during childhood. In a more recent study, Nylander and Gillberg (2001) screened for autism spectrum disorders in a sample of psychiatric outpatients. Those with schizophrenia were most likely to also be diagnosed with autism spectrum disorders compared to individuals with other psychiatric disorders. However, other studies have shown conflicting results. Specifically, Volkmar and Cohen (1991) studied 163 adolescents and adults with well-established histories of autism. They found that among these individuals, only one person had a history of schizophrenia as well. This study demonstrated that autistic disorder and schizophrenia do not commonly appear together, and that individuals with autistic disorder are at no greater risk for schizophrenia when compared to individuals in the general population.

However, using both a categorical and dimensional approach to schizophrenia, Konstantareas and Hewitt (2001) found that 50% of individuals with AD also presented with the disorganized characteristics of schizophrenia, although individuals with schizophrenia were not likely to present with features of AD. However, when Sheitman and colleagues (2004) examined individuals with treatment-resistant schizophrenia, using the Autism Behavior Checklist (ABC),

their findings indicated the existence of autistic symptoms in these individuals. Furthermore, these autistic symptoms co-varied with the negative symptoms of schizophrenia, which raises questions about the comorbidity of autistic and negative symptoms in individuals with a severe form of schizophrenia (Sheitman, Bodfish, & Carmel, 2004). Taken together, these studies show conflicting support for the notion of comorbidity of schizophrenia and AD, but do indicate some support for the notion that individuals with either disorder can show evidence of having characteristics of both disorders. This idea points to a final question, which concerns the diagnostic overlap between the two disorders, and this issue remains unclear. Questions remain about the potential for shared underlying etiologies, which could serve as explanations for the shared characteristics of the two disorders.

Phenomenologic Overlap Between Schizophrenia and Autistic Disorder

Motor abnormalities in schizophrenia and AD. Regarding motor abnormalities, individuals with schizophrenia show deficits in motor skills both before and after the onset of the illness. As previously discussed, Walker (1994) was able to demonstrate the pre-schizophrenic children can be distinguished from their healthy siblings on the basis of the abnormal movements. There is also evidence that these motor abnormalities continue after the onset or phenotypic expression of schizophrenia occurs. In a review of neuromotor abnormalities in schizophrenia, Marsden (1982) highlighted involuntary motor disturbances in schizophrenia that include involuntary jerky movements, perserverative errors, abnormal muscle tonicity, and writhing movements. Subsequent studies have revealed significantly poorer motor performance or deficits in motor functioning in individuals with schizophrenia (Heinrichs & Zakzanis, 1998; Schwartz et al., 1990). Other studies have shown that these motor abnormalities are independent of treatment with antipsychotic medications (Caligiuri, Lohr, & Jeste, 1993; Gupta et al., 1995).

Similar to individuals with schizophrenia, individuals with AD also display difficulties with motor performance and evidence of motor abnormalities. Jones and Prior (1985) found that children with AD displayed difficulties with motor imitation tasks, including performing

coordinated movements, when compared to normal children. In two studies similar to the Walker (1994) study, motor abnormalities and movement disturbances in the shaping of the mouth as well as the difficulties with the development of major motor milestones such as crawling and sitting were evidenced in the home videos of infants who were later diagnosed with AD (Adrien et al., 1991; Teitelbaum et al., 1998). Other studies have indicated similar difficulties with motor performance in children diagnosed with autistic disorder (Ohta et al., 1987; Ornitz et al., 1977; Rapin, 1997; Rinehart, Bradshaw, Brereton, & Tonge, 2001).

Cognitive and language impairment in schizophrenia and AD. Schizophrenia and AD also share characteristics of cognitive impairment. As previously indicated, pre-schizophrenic individuals suffer from lower intellectual functioning, poor performance on educational tests, and language-based deficits; however, these impairments are also evident after the onset of schizophrenia. Cognitive impairment is a hallmark symptom of schizophrenia (Walker & Walder, 2003), and is not due to the secondary effects of medication, hospitalization, or positive and negative symptoms (Hoff & Kremen, 2002; Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000; Kremen, Seidman, Faraone, & Tsuang, 2001). Cognitive deficits in schizophrenia include impairment in multiple domains, including attention (Bozikas, Kosmidis, Kiosseoglou, Karavatos, 2006; Lieh-Mak, 1997), executive functioning (Weickert et al., 2000), verbal memory (Compton et al., 2006; Rund et al., 2006), verbal declarative memory (Kremen et al., 2001), working memory (Bozikas et al., 2006) and verbal fluency (Docherty et al., 1996).

Although difficult to separate from underlying processes of cognition and formal thought disorder, individuals with schizophrenia also suffer from numerous language-based deficits. An early study in this area found that an individual suffering from a psychotic episode also experienced impairments in language that included ordinary speech errors, aphasia, and a distraction by the sounds of particular words (Chaika, 1974; Covington et al., 2005). Studies and reviews of language-based impairments in schizophrenia have discovered widespread evidence for disturbances in language comprehension, production, attention, and cerebral lateralization of

language (Bagner, Melinder, & Barch, 2003; Condray, Steinhauer, van Kammen, & Kasparek, 2002; DeLisi, 2001). Individuals with schizophrenia also use neologisms (making up new words; Andreasen, 1979; McKenna, 1994) and suffer from word-finding difficulties such as word approximation (McKenna, 1994).

Cognitive impairment is also a common symptom of AD, although impairment is at times difficult to ascertain due to the severe language impairments in autistic disorder. However, approximately 75% with AD are estimated to suffer from comorbid mental retardation, and they tend to scorer lower on measures of verbal intelligence, relative to nonverbal intelligence (Mayes & Calhoun, 2003). Regarding language abilities, many children with AD also suffer from language-based deficits. Impairments in communication, including a delay in or lack of language development, use of repetitive or stereotyped language, and an inability to initiate or sustain conversations, are a main deficit in AD. Language impairments are typically one of the earliest complaints of parents with children who are later diagnosed with AD (De Giacome & Fombonne, 1998). Substantial subgroups of autistic individuals never develop language at all, and those who do speak typically suffer from impairments such as unusual intonation, difficulties with pragmatics, echolalia, and pronoun reversal (Lord & Paul, 1997). Furthermore, a recent study with individuals with high-functioning autism revealed significant difficulties with expressive grammar and figurative language (Landra & Goldberg, 2005).

Social functioning in schizophrenia and AD. A final similarity between schizophrenia and AD concerns the social functioning of individuals with either of these two disorders. Social functioning in schizophrenia is markedly impaired and is categorized as part of the constellation of impairments in one or more major areas of life functioning. This is important because social functioning contributes to overall functional outcome and ability to function in a community setting. Early research on the social functioning of individuals with schizophrenia has focused on deficits in this area of functioning (Argyle, 1981; Bellack, Morrison, Wixted, & Mueser, 1990), and has continued in the past two decades. Yager and Ehmann (2006) highlight the confusion of

defining social functioning in schizophrenia, and report on how researchers tend to measure varying attributes when investigating social functioning. They include Green's (1996) definition of social functioning when compiling these many attributes: independent living, employment, interpersonal relationships, and recreation. However, for the purposes of this review, a focus is placed on social functioning in association with other individuals, including interpersonal functioning, emotional functioning, and the formation of interpersonal relationships.

One area of research in this field concerns social perception abilities in individuals with schizophrenia. Social cue perception, which is the ability to accurately perceive social cues, involves both verbal and nonverbal behaviors as well as emotional perception. Individuals with schizophrenia have been shown to suffer from deficits in social cue perception (Archer, Hay, & Young, 1994; Corrigan, 1997; Edwards, Jackson, & Pattison, 2002; Murphy & Cutting, 1990). Individuals with schizophrenia also suffer from a lack of general social knowledge, including an inability to detect attributes of social situations (Cutting & Murphy, 1990). Furthermore, individuals with schizophrenia have difficulty with making eye contact with others and they suffer from deficits in the duration of verbal responses during social interactions, and turn-taking during conversations (Bellack et al., 1990; Bellack, Mueser, Gingerich, & Agresta, 1997; Davison, Frith, Harrison-Read, & Johnstone, 1996; Mueser, Bellack, Douglas, & Morrison, 1991).

Other research concerns difficulty with emotional processing in the context of social and interpersonal functioning. Schneider and colleagues (2006) found that individuals with schizophrenia were impaired in the ability to discriminate between emotional aspects of facial expressions and faces showing no emotion. This highlighted the notion that deficits in the area of emotional processing may contribute to difficulty with interpersonal and social interactions.

Social functioning is also greatly impaired in AD. According to the DSM-IV (2000), a diagnosis of AD includes abnormalities in nonverbal behaviors such as making eye contact, use of facial expressions, and posturing and gesturing. There is also impairment in the ability to form

peer relationships and friendships. Other criteria for meeting AD include a lack of enjoyment in interacting with other people, and a lack of social and emotional reciprocity. Several reviews of social-emotional functioning in AD have highlighted the trouble that children with AD have with social relationships, emotional awareness, and the social use of language (Loveland, 2005; Volkmar, Carter, Grossman, & Klin, 1997). Furthermore, Robertson and colleagues (1999) identified impairments in joint attention, affective reciprocity, and theory of mind in children with autistic spectrum disorders.

Some researchers have begun more advanced studies of the overlap between schizophrenia and AD in that they have moved beyond looking at symptoms and are examining other core features of the disorders. For example, Couture et al. (2010) investigated social cognition deficits in schizophrenia and high-functioning autism, and found that both groups scored lower on several measures of social cognition relative to a healthy control group. However, they could not be differentiated from one another on their scores. Furthermore, when the schizophrenia group was subdivided based on positive and negative symptomology, results showed that the high-functioning autism group was more similar to the negative schizophrenia group with respect to social cognition.

Schizophrenia and Schizotypal Personality Disorder

The above-reviewed research demonstrates clear and compelling overlaps between schizophrenia and AD. As previously mentioned, one method of studying the relationship between schizophrenia and AD is to examine associations among features of the milder ends of the spectrums of the two disorders. Regarding the schizophrenia spectrum, schizotypal personality disorder (SPD) has been said to be the prototype of schizophrenia spectrum disorders (Siever et al., 2003). It has been suggested that SPD may be a more common phenotypic expression of the underlying neural diathesis in the schizophrenia spectrum (Siever et al., 2003; Walker & Diforio, 1997).

Schizotypal personality disorder is comprised of a number of diagnostic criteria, including social and interpersonal deficits, cognitive and perceptual distortions, and eccentricities in behavior. Many of the prodromal signs of schizophrenia parallel the cardinal symptoms of SPD. As a cluster A (odd or eccentric) personality disorder, SPD is characterized by deficit-like, psychotic-like symptoms, cognitive-perceptual symptoms, and cognitive disorganization (Siever et al., 2002). These symptoms include ideas of reference, cognitive/perceptual distortions, magical thinking, social deficits, interpersonal symptoms, and cognitive disorganization or paranoid symptoms. The positive- and negative-like symptoms are thought to have separate pathophysiologies (Siever & Davis, 2004), much as they do in schizophrenia.

Schizotypal personality disorder can be an appropriate phenotype to study due its developmental, genetic, and biological relationships with schizophrenia. For many patients with schizophrenia, the prodromal phase of the disorder begins in adolescence; this prodromal period symptomatically resembles the clinical profile of SPD. It is believed that SPD likely represents an individual's developmental risk of schizophrenia. Like other personality disorders, SPD has a relatively stable course. However, it is estimated that between 25-45% of those diagnosed with SPD in adolescence go on to develop schizophrenia (Miller et al., 2002; Yung et al., 2003), once again highlighting the developmental link between the two disorders.

Regarding the genetic link, SPD occurs in about 3% of the general population (DSM-IV-TR, 2000), but it is far more common among first-degree biological relatives of individuals with schizophrenia (Tienari et al., 2003). Family, twin, and adoption studies have demonstrated the genetic association between SPD and schizophrenia (Nicolson et al., 2003; Tienari et al., 2003), and families of patients with SPD have an increased prevalence of schizophrenia spectrum disorders as well as schizophrenia itself (Battaglia et al., 1995). Similarly, the likelihood of having a relative with SPD is comparable for individuals whether they are diagnosed with SPD or schizophrenia (Silverman et al., 1993).

Regarding the biological link between schizophrenia and SPD, a recent qualitative review concluded that patients with schizophrenia and SPD show similar abnormalities in brain structure, particularly with regard to temporal regions. Within this region, both groups have decreased volumes in the superior temporal gyrus, and abnormalities in this area have been associated with cognitive disorganization and verbal learning (Siever et al., 2002). Additionally, SPD individuals have reductions in Heschl's gyrus and the inferior and middle temporal gyri. Decreased volume in these areas is associated with schizophrenia-related psychopathology (Siever & Davis, 2004). Additionally, both individuals with schizophrenia and SPD individuals have reduced activation in the frontal cortex. For SPD individuals, the reduced activation in the middle frontal gyrus is accompanied by greater activation in the right prefrontal cortex. It is not clear why SPD individuals activate additional brain regions not indicated in schizophrenia or normal comparison controls. Temporal lobe laterality is also apparent in schizophrenia and SPD, however less severe in the former (Siever & Davis, 2004). Furthermore, individuals with schizophrenia and SPD individuals show abnormalities in neurohormonal indicators of stress responsivity, or a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is thought to mediate stress and symptomology in schizophrenia.

Finally, individuals with schizophrenia display abnormalities in the functioning of several important neurotransmitters. However, research has also shown that SPD individuals also exhibit these abnormalities, namely in dopamine function. In both disorders, increased levels of dopamine are associated with psychotic symptoms and decreased levels are associated with deficit symptoms (Siever & Davis, 2004). Additionally, reduced dopamine in the prefrontal cortex is related to impaired performance on working memory tasks in individuals with schizophrenia. A neural diathesis-stress model, proposed by Walker and Diforio (1997), integrates the effects of heightened dopamine sensitivity on HPA dysregulation in individuals with schizophrenia and individuals with SPD.

Schizotypal Personality Disorder and Autistic Disorder

The research reviewed above demonstrates an association between schizophrenia and SPD. The important links between the two disorders gives credibility to the idea that SPD is a schizophrenia-spectrum illness that can be studied due to its approximation to the disorder of schizophrenia, as well as to the idea that SPD can be studied in relation to autistic-like features because of the phenomenologic overlap between schizophrenia and AD. Furthermore, SPD is potentially a beneficial area to study because individuals with the disorder are assumed to have a propensity to developing schizophrenia, but can be studied without the confounding effects of chronic schizophrenic illness or antipsychotic medications.

However, as previously mentioned, there have been only two studies that have examined the relationship between schizotypal features or SPD, and features of autistic-spectrum disorders. Hurst and colleagues (2007) studied the relationship between features of SPD and features of Asperger's disorder in a non-psychiatric sample of adults. Their results showed that scores from a self-administered questionnaire on Asperger's-related traits correlated positively with scores from a self-administered questionnaire on schizotypal traits. Furthermore, the social functioning and communication domains of the Asperger's questionnaire were strongly correlated with the interpersonal and disorganized domains of the schizotypal questionnaire, respectively. This study provided some of the first evidence for overlap between self-rated milder autistic-spectrum symptoms and milder schizophrenia-spectrum features in normal adults.

A second study, conducted by Esterberg and colleagues (2008), investigated childhood and current autistic features in a sample of adolescents diagnosed with SPD. These adolescents were compared to others with other personality disorders and normal adolescents. Their results indicated that adolescents with SPD showed more severe autistic features both during childhood and currently when compared to adolescents with other personality disorders and normal adolescents. Esterberg et al. (2008) also found that autistic features correlated positively with positive and negative prodromal psychotic symptoms, but that autistic features did not predict conversion to psychosis among those adolescents who had converted. Their findings provided

some of the first evidence that mild autistic features related to mild but diagnosable levels of schizotypy in a clinical sample.

The dearth of research in this area indicates a need for further investigation into the phenomenologic overlap between schizophrenia-spectrum and autistic-spectrum disorders, as well as further understanding of etiologic mechanisms that might account for this overlap. Early theorists in the field of psychopathology posited an etiologic relationship between autism and the psychoses (Bender, 1947). Both shared environmental and genetic risk factors have been proposed to account for the relationship (Kraemer, 1996). Among the environmental factors that have been suggested to account for this relationship are obstetrical complications and prenatal insults (Cannon et al., 2002; Glasson et al., 2004; Juul-Dam et al., 2001; Laviola, Adriani, Rea, Aloe, & Alleva, 2004), as well as fetal exposure to maternal viral infection (Brown et al., 2004; Ciaranello & Ciaranello, 1995; Miller et al., 2005; Rodier & Hyman, 1998). These environmental insults are likely to result in abnormalities in brain structure and function that are present in both schizophrenia and AD (Abi-Dargham, 2004; Abi-Dargham & Moore, 2003; Hendren et al., 2000; Grady & Keightley, 2002; Shenton et al., 2001; Volkmar, 2001).

Several types of obstetrical complications and prenatal insults have been linked to both autism and psychotic disorders such as schizophrenia. Cannon and colleagues (2002) conducted a meta-analysis of obstetrical complications and risk of schizophrenia, and found that pregnancy complications, including bleeding and diabetes, abnormal fetal growth and development, including low birth-weight and reduced head circumference, and delivery complications, including asphyxia and emergency Cesarean sections, significantly differentiated between mothers of individuals with schizophrenia and mothers of control subjects.

Similarly, Juul-Dam and colleages (2001) reported that mothers of children with AD were found to have a significantly higher incidence of uterine bleeding during pregnancy, and other studies reported that children with AD are more likely to have experienced fetal distress during birth and more likely to have been delivered by an elective or emergency cesarean section

(Glasson et al., 2004). Furthermore, animal models have shown that exposure to neonatal asphyxia leads to social withdrawal and stereotyped behaviors, both of which are common in schizophrenia and autistic disorder (Laviola et al., 2004).

Fetal exposure to maternal viral infection has also been linked to increased risk of schizophrenia and it has been hypothesized to be the primary non-genetic cause of AD (Ciaranello & Ciaranello, 1995). Although some studies have previously shown mixed support for the association between prenatal infection and schizophrenia (Bagalkote, Pang, & Jones, 2001), Brown and colleagues (2004) presented the first human serologic evidence that maternal influenza infection increases the risk of development of schizophrenia in offspring. Several studies have also shown that maternal viral infection during pregnancy is a risk factor in autism (Miller et al., 2005; Rodier & Hyman, 1998). A recent mouse model has shown that prenatal exposure to maternal influenza virus produces highly abnormal behavior that is akin to what is seen in schizophrenia and autistic disorder, including atypical social interaction, deficits in prepulse inhibition, and reduced exploratory behavior (Shi, Fatemi, Sidwell, & Patterson, 2003). This research group also showed that maternal infection specifically alters the expression of a subset of genes in the brain, which subsequently influences changes in brain structure and function (Fatemi, Pearce, Brooks, & Sidwell, 2005).

Research in molecular genetics has also provided evidence for potential shared or common pathways to schizophrenia- and autistic-spectrum disorders. One such area has included the study of copy number variation (CNV), which refers to insertions, duplications, deletions, or allelic rearrangements of particular genes. A recent review demonstrated that spontaneous or *de novo* deletions and duplications are involved in the development of autism, with several locations in the genome being identified as potentially important (Kusenda & Sebat, 2008). Other studies have shown support for the involvement of *de novo* CNVs in the development of schizophrenia and other psychotic disorders. For example, Stefansson et al. (2008) found that *de novo* deletions at three chromosomal loci were associated with schizophrenia in a large Icelandic sample.

In a recent review of the involvement of CNVs in neuropsychiatric disorders, Cook and Scherer (2008) conclude that research on CNV has demonstrated that common genes account for the development of different psychiatric disorders, and that rare CNVs have been shown to account for a portion of the genetic predisposition to disorders such as schizophrenia and autism. Furthermore, while they acknowledge that it may be due to chance that there is overlap of CNVs in schizophrenia and autism, it could be that the genes involved in both disorders show variable expressivity (i.e., genes for autism also confer susceptibility to milder forms of autism or related disorders) or are pleiotropic, meaning that they exert multiple effects. This could offer an etiological explanation for the strong similarities between the two spectrums.

Other areas of potential research include explorations of candidate genes that are involved in the development of both schizophrenia and AD. One line of investigation that is of particular significance is research on individuals with 22qDS, a genetic disorder with a variable psychiatric phenotype that includes psychotic symptoms, mood disorders, attention deficit disorders, as well as autistic-spectrum disorders. Understanding more about the pathways that lead to the greater prevalence of schizophrenia and AD in individuals with this genetic disorder could shed light on etiologic mechanisms involved in these psychiatric illnesses.

22q11.2 Deletion Syndrome

Occurring in 1 out of 4,000 births (Wilson et al., 1994), 22qDS, one of the most common genetic disorders, is caused by a deletion of approximately three million base pairs on one copy of chromosome 22. This deletion is located on the long arm of chromosome 22, and results in the microdeletion of around 30 to 40 genes. Most cases of 22qDS are not inherited, but inheritance of 22q11 deletion syndrome is considered to be autosomal dominant. The majority of 22qDS cases occur spontaneously through genetic mutations.

22qDS has also been referred to as velo-cardio-facial syndrome, DiGeorge syndrome, and conotruncal anomaly face syndrome, with each of these conditions being associated with a different set of features and characteristics that are all part of the 22qDS phenotype. Among

these features are physical signs and symptoms, including heart defects, cleft palate, immune deficiencies, skeletal abnormalities, and minor facial anomalies. As mentioned earlier, individuals with 22qDS also show an increased prevalence of psychiatric disorders, including schizophrenia and other psychotic disorders, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, and autistic-spectrum disorders (Antshel et al., 2007; Gothelf et al., 2004; Gothelf et al., 2007; Zagursky et al., 2006).

Psychiatric Phenotype of 22q11.2 Deletion Syndrome

As mentioned above, individuals with 22qDS show a high prevalence of behavioral disturbances and psychiatric disorders. Baker and Skuse (2005) compared individuals with 22qDS to matched control participants, and found that disorders such as ADHD, depression, and anxiety, as well as transient psychotic symptoms were more common in those with the deletion syndrome. Arnold and colleagues (2001) compared individuals with 22qDS to their non-deleted, age-matched siblings, and found that mood disorders were significantly more common among those with the deletion compared to their siblings. Furthermore, 22qDS individuals displayed significantly higher schizotypal symptoms, ADHD-related features, separation anxiety, and depressive symptoms compared to their siblings.

Several reviews of the research on psychiatric difficulties in 22qDS have echoed the findings from studies such as those reviewed above. For example, a recent review by Prasad, Howley, and Murphy (2008) showed that temperament and behavior problems were common in 22qDS children and adolescents; these include problems with social skills and interaction, extreme inhibition or impulsivity, attachment problems, and separation anxiety. They also cite research that has demonstrated that ADHD is present in up to half of children with the deletion syndrome, and note that children and adults with 22qDS show high rates of affective and anxiety-related disorders, including obsessive-compulsive disorder. Finally, and of most relevance to the current study, Prasad and colleagues (2008) review research that has demonstrated that children

and adults show high rates of psychotic disorders, including schizophrenia, as well as autistic-spectrum disorders.

Psychotic Disorders and Schizophrenia. Shprintzen and colleagues (1992) first described the presence of psychotic symptoms in a sample of children and adults with 22qDS. Subsequent studies have shown that schizophrenia is the most prevalent psychiatric disorder in adults with 22qDS, with approximately 25% of individuals with 22qDS meeting diagnostic criteria for schizophrenia (Bassett et al., 2005; Murphy et al., 1999). Gothelf et al. (2007) compared 31 children with 22qDS to 29 matched children with idiopathic developmental disabilities, and found that over 30% of the former group had developed psychotic disorders after a five-year follow-up.

Murphy, Jones, and Owen (1999) studied 50 adults with velo-cardio-facial syndrome, 48 of whom were shown to have the 22q11.2 deletion. Of these 50 subjects, nearly half had a history of a major psychiatric disorder, and 30% of the overall sample had a history of psychosis. Baker and Skuse (2005) studied 50 adolescents and young adults, 25 of who had 22qDS, and 25 who were age- and IQ-matched controls. Their findings showed that 79% of the 22qDS sample met criteria for one or more DSM-IV psychiatric disorder, compared to 21% of the matched controls. While schizophrenia was not specifically examined, adolescents with 22qDS showed significantly higher scores on a measure of schizotypy relative to the matched control sample, and 84% of adolescents with 22qDS endorsed at least one schizotypal symptom. Finally, Debbane and colleages (2006) studied 43 children and adolescents with 22qDS, and found that 28% of the sample showed psychotic symptoms.

Only one study has specifically examined prodromal symptoms in 22qDS youth, which, according to Cannon et al. (2008), are most reliably associated with increased clinical risk for schizophrenia. Stoddard et al. (2010) studied 20 adolescents using the SIPS. Findings from this study indicate that a greater percentage of adolescents experienced moderate to severe levels of negative (85%), disorganized (55%), and general (60%) symptoms relative to the percentage of

adolescents experiencing positive (45%) symptoms. To date, this has been the first evidence to suggest that non-psychotic adolescents with 22qDS experience moderate to severe prodromal symptomology.

Also of interest is that not only do schizophrenia-spectrum disorders appear to be more common in individuals with 22qDS compared to the general population, but also that 22qDS appears to be more common in individuals with schizophrenia relative to non-clinical samples. A recent review conducted by Bassett and Chow (2008) indicated that while 22qDS tends to occur in about 1 in 4000 live births in the general population, the deletion syndrome can be found in around 1 in 100 individuals with schizophrenia (Bassett & Chow, 2008; Horowitz, Shifman, Rivlin, Pisanté, & Darvasi, 2005). Given that an increased rate of schizophrenia-spectrum disorders is seen in 22qDS, and an increased rate of 22qDS exists in individuals with schizophrenia-spectrum disorders, it is clear that a significant association is present between the two clinical syndromes.

Autistic-Spectrum Disorders. Autism-spectrum disorders have also been found to be prevalent in individuals with 22qDS. One of the more recent studies, conducted by Antshel and colleagues (2007), studied 41 children with velo-cardio-facial syndrome, all of whom had a 22q11 deletion. Using the Autism Diagnostic Inventory-Revised (ADI-R; Lord, Rutter, & LeCouteur, 1994), findings showed that 42% of the subjects met criteria for an autism-spectrum disorder, with eight children of the 41 meeting criteria for autism. Interestingly, this sample of children and adolescents was recruited for a longitudinal study of risk factors for psychosis.

Another study, conducted by Vorstman and colleagues (2006), evaluated 60 patients with 22qDS between the ages of 9 and 18 years also using the ADI-R to assess autistic-related symptoms. Half of the sample was diagnosed with a DSM-IV autism-spectrum disorder, including autism and pervasive development disorder, not otherwise specified. Furthermore, over 11% (n = 7) of the sample was diagnosed with a psychotic disorder, including schizophrenia, and the majority of these subjects, five of seven, were comorbid for an autism-spectrum disorder.

Fine and colleagues (2005) studied 98 children between the ages of two and 12 with 22qDS with respect to ALB. Prior to the study, caregivers of each child completed screening questionnaires, and if children were rated above an a prior cut-off score on the screening measure or had been previously diagnosed with an ASD participated in a second study which utilized the ADI-R to rate each child's functioning. Results showed that eight of the children had been previously given an ASD diagnosis, and a total of 22 children met criteria to be rated with the ADI-R. Of the 20 participants for whom caregivers completed the ADI-R, 11 qualified for a diagnosis of autism, and another 3 met criteria for a more broadly defined ASD. Approximately 14% of the overall sample (n = 14) met criteria for an ASD.

Niklasson et al. (2001) studied 32 children and young adults with 22qDS using the Asperger Syndrome Screening Questionnaire (ASSQ; Ehlers, Gillberg, & Wing, 1999); scores of 16 and higher indicate high likelihood that a child is suffering from a pervasive developmental disorder or autism spectrum disorder. Results showed that the mean ASSQ score of the sample was 14.7, with 12 of the sample having scores of 16 or greater. Nine of these 12 children received diagnoses of pervasive developmental disorder, not otherwise specified, or autistic disorder. Finally, Rouberie et al. (2001) conducted a study of three children with 22qDS. Of these three children, one was diagnosed with DSM-IV autism due to the appearance of behavioral disturbances when the child was 23 months of age. These disturbances included limited eye contact, decrease in emotional range, poor social skills, lack of shared enjoyment and joint attention, limited vocabulary, stereotypies, and lack of peer relationships.

In summary, the literature reviewed above provides evidence that schizophrenia-spectrum disorders, ASD, and ALB are all highly prevalent in individuals with 22qDS. The high prevalence of both psychotic disorders and ASD in individuals with 22qDS suggests a relationship between the two diagnostic entities, and raises questions about etiologic overlap. However, more research is needed to understand this phenomenon, especially research utilizing well-defined control groups, including both normal and clinical controls, in order to compare the

prevalence and severity of ALB. Such research will shed light on differences and similarities among various psychiatric risk groups with respect to ALB.

Catechol-O-methyltransferase (COMT)

One of the genes in the deletion region of the 22qDS encodes for the enzyme *catechol-O-methyltransferase* (COMT). This gene has also been implicated in risk for schizophrenia. As a result, this gene has been the focus of research aimed at elucidating its phenotypic manifestations. The COMT gene encodes for two forms of the enzyme: a soluble cytoplasmic isoform (S-COMT) that is located predominately in peripheral tissues, and a membrane-bound isoform (MB-COMT) that resides in the brain (Jeffrey & Roth, 1984; Tenhunen et al., 1994). Although dopamine transporters are the primary mechanisms for the degradation of catecholamines such as dopamine, COMT is also responsible for the breakdown of dopamine, especially in areas such as the prefrontal cortex, where there is a low concentration of dopamine transporters (Craddock, Owen, & O'Donovan, 2006; Lewis et al., 2001). Given that COMT is located in the deletion region of 22qDS, individuals with 22qDS carry only one copy of the gene and are therefore *hemizygous* for COMT.

The gene encoding for MB-COMT contains a single nucleotide polymorphism (SNP), or a variation in the DNA sequence; this G-to-A polymorphism results in a valine-to-methionine (Val/Met) substitution at codon 158 of the protein (correspondingly, codon 108 of S-COMT). This polymorphism has been referred to as the $Val^{158}Met$ polymorphism or as *rs4680*, the reference sequence identification code (Craddock et al., 2006). The two alleles show differential levels of activity with respect to dopamine degradation. The Val allele is known as the high activity allele; individuals who are homozygous for COMT Val show approximately 40% more activity in the breakdown of dopamine, which results in lower concentrations of dopamine in the prefrontal cortex (Chen et al., 2004). The Met allele is known as the low activity allele, which results in greater concentrations of dopamine due to less degradation (Chen et al., 2004). The role of COMT in the catabolism of dopamine has made it a prime target of investigation of potential

candidate genes for particular psychiatric disorders in which the role of dopamine is especially important in their pathophysiology.

COMT and Schizophrenia. COMT is of particular relevance to schizophrenia because of the well-documented involvement of dopamine in the pathophysiology of psychosis. In a recent review of the molecular mechanisms involved in schizophrenia, Lang and colleagues (2007) discuss the "dopamine hypothesis" of schizophrenia, which posits that greater concentrations of dopamine in the mesolimbic and striatal brain areas are associated with more severe positive symptoms, while decreased concentrations of dopamine in the prefrontal areas of the brain are correlated with more severe negative symptoms. Support for this hypothesis is found in studies that have demonstrated that antipsychotic medications exert their effects on the symptoms of schizophrenia because they are primarily antagonists or partial agonists of dopamine D2 receptors.

Further support for the dopamine hypothesis of schizophrenia is found in studies showing that dopamine-enhancing drugs such as amphetamines and L-DOPA can induce or exacerbate psychotic symptoms. Experimental studies during the 1970's demonstrated that prolonged use of psychostimulants resulted in psychotic symptoms in non-clinical individuals (Angrist & Gershon, 1970; Bell, 1973). Lieberman et al. (1987) reviewed studies that showed a state-dependent response to dopamine-enhancing psychostimulants in individuals with schizophrenia, such that these drugs induced or worsening psychotic symptoms.

Given that dopamine has been shown to play a role in schizophrenia symptoms, and that COMT has been found to be involved in dopamine degradation, researchers have naturally turned toward investigating COMT as a potential candidate gene for schizophrenia. There has been a particular emphasis placed on the $Val^{158}Met$ polymorphism of COMT, given the functional effect of this polymorphism on enzyme activity. However, linkage studies that have investigated susceptibility loci (implicating chromosome 22) for schizophrenia as well as association studies with COMT as a candidate gene have provided mixed results.

Glatt, Faraone, and Tsuang (2003) cited the lack of consistency in the findings of studies attempting to identify COMT as a susceptibility gene for schizophrenia, and conducted a meta-analysis of these studies to determine if the failure to identify an association was due to small sample sizes, low statistical power, or etiological heterogeneity. Their results showed that the pooled odds ratio for the case-control studies showed no association between either allele and schizophrenia. However, the meta-analysis for the family-based studies showed that there was some evidence for the Val allele to be associated with development of schizophrenia. Glatt and colleagues (2003) also concluded that ethnicity was a moderator; the Val allele appears to be more of a risk factor in individuals of European ancestry, and less of an influence in Asian populations.

A more recent meta-analysis conducted by Munafò and colleagues (2005) attempted to replicate the findings of Glatt et al. (2003), and included more studies and advanced statistical analyses. Their findings showed that the Val allele of COMT was significantly associated with patient status; they also found a main effect of European ancestry. However, when Munafò et al. (2005) conducted a second analysis excluding studies that reported allelic frequencies that departed from the Hardy-Weinberg equilibrium, their results showed that COMT was *not* significantly associated with schizophrenia.

Although the above results suggest that COMT is not associated with risk for schizophrenia, as currently defined, COMT continues to be of interest to researchers studying heterogeneity in the disorder. Craddock and colleagues (2006) cite support for a relationship between COMT and frontal lobe function, both in normal controls and individuals with schizophrenia. Furthermore, a recent review by van Haren, Bakker, and Kahn (2008) discussed reports of associations between the COMT Val/Met polymorphism and brain structure and functioning, including reduced volumes of the anterior cingulate gyrus and medial temporal gyrus in homozygous Val patients with schizophrenia (Ho, Wassink, O'Leary, Sheffield, & Andreasen, 2005, McIntosh et al. 2007, and Ohnishi et al., 2006, as cited in van Haren, Bakker, & Kahn,

2008). These results are consistent with other reports implicating COMT in the cognitive deficits seen in patients with schizophrenia (Egan et al., 2001; Goldberg et al., 2003; Joober et al., 2002), with some evidence that the Val allele is associated with poorer cognitive functioning.

Of relevance to the current study is the possible relationship between COMT and symptoms of schizophrenia. Similar to other areas of study of COMT, findings are mixed. For example, Goghari and Sponheim (2008) studied patients with schizophrenia, and found that COMT genotype was associated with lifetime positive symptomatology, with homozygous Val and heterozygous patients showing greater lifetime positive symptoms, relative to homozygous Met patients. Others have found no association between symptom severity in schizophrenia and COMT genotype for the Val^{158}Met polymorphism. For example, Strous et al. (2006) found that PANSS scores did not vary with respect to COMT genotype, and others have found similar results (Numata et al., 2007; Tsai et al., 2004).

However, the majority of studies that have examined the relation of COMT with symptom severity indicate that the Met allele is linked with greater severity. Bilder and colleagues (2002) studied the impact of COMT on positive and negative symptoms, and showed that there was a trend for homozygous Met patients to have the highest total and negative symptom PANSS scores. Herken and Erdal (2001) found that patients who were homozygous for the Met allele had more severe symptoms relative to heterozygous patients and patients homozygous for the Val allele. Han et al. (2006) studied 132 male patients with first-episode schizophrenia-spectrum disorders and found that the Met allele was associated with more severe delusions. Finally, Inada, Nakamura, and Iijima (2003) found that patients homozygous for the Met allele received a significantly higher daily neuroleptic dosage compared to Val/Met and Val/Val patients, and there was a trend for Met/Met patients to show a higher rate of treatment resistance.

In a discussion of factors that might account for the contradictory findings, Goghari and Sponheim (2008) hypothesize that the mixed findings regarding the association between

symptoms and COMT could be due to the use of cross-sectional measures of symptoms, which are influenced by episodic changes in schizophrenia, as well as effects of antipsychotic medications on symptom severity. This is a valid and important point: any association between the severity of symptoms and COMT genotype may be obscured by the fact that symptom severity and adverse side effects typically determine antipsychotic dosage. Thus, current symptom severity in medicated patients may be determined more by pharmacologic treatment than by genetically determined neurobiologic aspects of their illness.

Therefore, it may be optimal to examine the relation of COMT with pretreatment symptom severity or with schizophrenia-spectrum symptoms in at risk individuals who do not manifest the full clinical disorder. In this case, the relationship would likely not be influenced by transient changes in clinical states or confounded by the use of medications. Specifically, Fanous and Kendler (2004, 2005) advocate for the investigation of schizotypy as an intermediate phenotype in the investigation of genes such as COMT that are potentially involved in vulnerability to schizophrenia.

COMT and Schizotypy. Five studies have directly examined the association between schizotypy and COMT genotype, specifically the Val^{158}Met polymorphism. Avramopoulos and colleagues (2002) studied 379 males with respect to variation in schizotypal symptoms. Findings showed that subjects homozygous for the high activity (Val) allele scored significantly higher on both the SPQ and the PAS, indicating more schizotypal symptoms. Homozygous Val subjects scored significantly higher on the SPQ and PAS relative to heterozygous Val/Met subjects; however, homozygous Val subjects scored higher than homozygous Met subjects only on the SPQ. In an extension of this study, Stefanis and colleagues (2004) studied 543 males and found that Val allelic loading was associated with higher total SPQ scores, but further analyses showed that this relationship was only significant in the negative and disorganized schizotypal dimensions.

Schürhoff et al. (2007) investigated 106 unaffected, first-degree relatives of patients with schizophrenia, first-degree relatives of patients with bipolar disorder, and healthy controls. Results showed that subjects who were homozygous for the high activity (Val) allele displayed more schizotypal symptoms compared to subjects homozygous for the low activity (Met) allele. However, heterozygous subjects did not differ with respect to total SPQ scores from homozygous Met subjects or homozygous Val subjects. Schürhoff et al. (2007) also found that symptom *dimensions* were associated with genotype, such that homozygous Val subjects showed more positive schizotypal symptoms compared to both Val/Met and Met/Met subjects, and the Val/Met subjects showed more positive symptoms relative to Met/Met subjects. Similar results were seen with the negative schizotypal dimension, although there was no difference between Val/Met and Met/Met subjects.

Contrary to the above findings, others have found that it is the low activity Met allele of COMT, and not the Val allele, that is associated with greater schizotypal symptoms. Sheldrick and colleagues (2008) studied 522 university students, using the brief version of the SPQ (SPQ-B; Raine, 1991). Results showed that subjects with the Met/Met genotype had higher scores on the disorganization dimension of the SPQ-B compared to subjects homozygous for the Val allele.

Ma and colleagues (2007) studied schizotypal symptoms of 465 healthy adults using the SPQ. Results showed that *in males only*, individuals homozygous for the high activity (Val) allele showed the lowest total SPQ scores and lowest scores on the disorganization dimension of the SPQ. Those male subjects who were heterozygous had the highest total and disorganized SPQ scores. Controlling for demographic variable such as age and education, the authors found that COMT genotype significantly influenced total SPQ score, as well as scores on the disorganization and constricted affect dimensions (Ma et al., 2007).

In summary, the results of research on the relation between COMT and schizotypal symptoms have yielded mixed results. However, it is possible that sex is contributing to the discrepancy. With the exception of one report (Schürhoff et al., 2007), all of the studies that find

a link between the COMT Val allele and greater symptom severity were based on samples of males only. Moreover, the one study that examined sex differences showed that the relation between the Val allele and symptom severity was restricted to males only (Ma et al., 2007). Thus, sex may moderate the relation between COMT genotype and symptom severity.

Several investigations have turned toward examining the relationship between COMT and schizophrenia-spectrum disorders in the context of 22qDS. For example, Gothelf and colleagues (2005) longitudinally studied 24 subjects with 22qDS, evaluated during childhood and again during late adolescence or early adulthood. These subjects were matched to a control group with idiopathic developmental disabilities. At follow-up, nearly 30% of the subjects had developed a psychotic disorder, and psychotic symptoms as measured by the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) were associated with COMT low-activity Met allele, but only in the 22qDS subjects. Furthermore, the low-activity allele of COMT was associated with a significantly greater decrease in prefrontal cortex gray matter volume relative to the high-activity allele. The authors concluded that COMT genotype plays a role in PFC gray matter volume decline and emergence of psychotic symptoms in early adulthood in patients with 22qDS (Gothelf et al., 2005).

In a similar study, Bassett and colleagues (2007) examined 73 adults with 22qDS; 33 of whom were diagnosed with a schizophrenia-spectrum disorder. The Val^{158}Met polymorphism of COMT was examined with respect to diagnostic status and positive and negative symptoms. Findings showed that while the Met allele of COMT was not significantly more common in 22q DS adults with schizophrenia, the Met allele was associated with more severe symptom scores, but only with respect to excitement symptoms and global functioning. Furthermore, the Met allele was associated with poorer performance on tasks measuring theory of mind, olfactory identification, and visual-spatial ability.

Bassett et al. (2007) posit that the inconsistent findings from studies in this area may be a function of age-dependent effects of COMT on symptom expression in individuals with 22qDS.

Specifically, she suggested that COMT genotype may impact symptom expression differentially at various ages of development, and this could be related to age-related changes in dopaminergic system. For example, De Keyser et al. (1990) found an age-related loss of neurons in the nigrostriatal dopaminergic system in postmortem human brains. Using positron emission topography (PET) and magnetic resonance imaging (MRI), Ota et al. (2006) more recently found that dopamine synthesis in the striatum as well as extrastriatal areas of the brain decreases with age. Even more relevant is a recent study with pre- and post-adolescent rats, which showed changes in the effect of dopamine on neurons in the prefrontal cortex during adolescence (Tseng & O'Donnell, 2007). Thus, the 22qDS and genes involved in the disorder continue to be viable model systems for studying the development of schizophrenia, given the heightened risk for the disorder among individuals with the deletion syndrome and the genetic homogeneity of the disorder.

COMT and Autistic Disorder. To date, only one study has examined the relation between COMT and autistic disorder. James and colleagues (2006) emphasized the metabolic basis for the development of autistic disorder, and studied a single metabolic pathway that has been implicated in other neurological disorders. James et al. (2006) posited that this pathway can be altered by changes in gene expression, and studied functional candidate genes that likely have an effect on these processes. Included in this study was a focus on the polymorphism 472G > A of COMT. Following metabolic and genetic analyses, results showed that the Val allele was significantly more frequent among autistic children compared to unaffected control subjects, and homozygous Val genotype was associated with an increased susceptibility to autistic disorder. No analyses were conducted to examine relations among genotype and autistic symptoms. There have been no other studies that have examined COMT as a candidate gene with respect to autistic-spectrum symptoms.

Summary

The above review demonstrates compelling evidence for a phenomenological overlap between schizophrenia spectrum disorders and autistic spectrum disorders, and sheds light on potential common etiological mechanisms. While questions remain about the exact nature of the overlap, there is significant evidence showing that individuals with schizophrenia-spectrum disorders, including those with SPD, are at increased risk for more severe ALB when compared to normal, non-psychiatric individuals or individuals with other psychiatric disorders. In particular, individuals with schizophrenia-spectrum disorders are more likely to show more severe deficits in the areas of social functioning and behavioral stereotypies and unusual interests, two main criteria for an autism-spectrum diagnosis.

In addition to phenomenological overlap, there is increasing evidence of shared etiologic factors, including prenatal complications, such as viral infections, and genetic mutations. Most noteworthy, studies of individuals with 22qDS indicate that they are at increased risk for a range of both schizophrenia and autistic-spectrum disorders. Thus, a deletion located on the long arm of chromosome 22, which results in the microdeletion of around 30 to 40 genes, heightens risk for disorders in both spectra, suggesting some proximal or overlapping risk genetic risk factors.

Finally, the above review presents evidence for a link between genes located in the deletion region of 22qDS and symptoms of schizophrenia as well as autistic disorder. While the literature in these areas is small and mixed, there is some evidence that COMT may play a role in the phenotypic overlap between the two disorders, and that the nature of the relation may vary with age.

These trends in the research findings suggest that studies of the developmental and phenomenologic characteristics of groups at clinical versus genetic risk for schizophrenia- and autistic-spectrum disorders may be fruitful. In particular, it is of interest to know whether the autistic-spectrum symptoms manifested by SPD and 22qDS patients differ with respect to severity, pattern, or developmental course. Similarly, examination of schizophrenia-spectrum

symptoms in these two disorders will provide insight into developmental similarities and differences between the two diagnostic groups.

To date, there have been no studies comparing the nature or severity of ALB in SPD and 22qDS patients. In order to address this gap in our understanding of these risk groups, the present study uses standardized measures to examine both autistic- and schizophrenia-spectrum symptoms in individuals with 22qDS and adolescents with SPD. Specifically, this study aims to determine whether there are symptoms or groups of symptoms that distinguish the two groups. The present study will also explore the relationships of psychotic and autistic features with COMT genotype in both diagnostic groups.

Hypotheses and Research Questions

1. It is hypothesized that the 22qDS group will show more severe early childhood autistic features relative to the SPD and healthy control groups, and the SPD sample will show more severe childhood autistic features relative to control participants.

2. It is also hypothesized that the 22qDS sample will show more severe *current* autistic features relative to the SPD and control groups, and the SPD sample will show more severe current autistic features relative to control participants. This hypothesis is based on literature showing that up to approximately 40% of 22qDS individuals also concurrently meet criteria for a diagnosis of an autism-spectrum disorder. While prior research has demonstrated that individuals with SPD are more likely than controls to show more severe ALB, there is no such evidence that they are more likely to be diagnosed with an autism-spectrum disorder.

3. It is anticipated that the SPD and 22qDS groups will not differ on prodromal symptoms given the heightened risk for developing schizophrenia between both diagnostic groups. However, it is hypothesized that both the SPD and 22qDS groups will show significantly more severe prodromal symptoms relative to control participants.

4. It is predicted that current autistic features, as measured by the ADI-R, and current prodromal symptoms, as measured by the SIPS, will be positively correlated. Thus, more severe autistic features will be linked with more severe prodromal symptoms.

5. For purposes of identifying possible homogenous subgroups within the 22qDS and SPD samples cluster analysis was conducted based on autistic features and prodromal symptoms. Thus, the cluster analysis has the potential to reveal syndromal subgroups that may differ in etiological processes.

6. Discriminant function analysis will be conducted to empirically determine whether there is an optimal combination of symptom variables that distinguishes between the two clinical groups, and achieves classification significantly above chance level

7. Finally, the relationship between COMT genotype and autistic and prodromal symptoms was examined. In the first set of analyses, potential effects of COMT genotype on symptoms in control and SPD participants were examined, given that both groups have two copies of the gene encoding for COMT. The second set of analyses tested effects of COMT genotype on symptoms in both SPD and 22qDS participants, utilizing all 22qDS participants and only homozygous SPD participants. Given the evidence of sex differences in the relation of COMT with symptoms, sex was included as a variable in these analyses.

Method

Participants

SPD and Control Sample. Participants of the SPD and healthy control samples consist of 77 adolescents ranging from 11 to 18 years of age. These adolescents were drawn from a large, longitudinal research study on biological and behavioral markers of SPD. Participants were recruited through newspaper announcements aimed at parents and through the Emory University Research Participant Registry. The present study included all adolescents who were assessed at least once at baseline with the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994). At baseline assessment, diagnostic assessments were administered, and

participants fell into two diagnostic categories: SPD (n = 30; 28.6% of overall sample) or healthy controls (n = 47; 44.8% of overall sample). Exclusion criteria for both the SPD and healthy control groups were a neurological disorder, mental retardation, current substance abuse/addiction, and any Axis I disorder. Thus, the SPD group did not include individuals who met Axis I criteria for any psychosis or autistic-spectrum disorder.

22qDS Sample. Participants were ascertained in reverse-age order from a case registry of individuals diagnosed with 22qDS. The case registry has been maintained at Children's Healthcare of Atlanta since 1996. Fluorescence In Situ Hybridization (FISH) was utilized to confirm the presence of the 22q11.2 deletion in each participant. Each individual was initially referred as either a child or adolescent, and each was referred due to the presence of heart defects, speech and language difficulties, and/or immunological problems. After initial recruitment, participants and their caregivers were interviewed at the Emory University 22qDS clinic, a collaborative treatment and research center maintained by researchers and physicians from Children's Healthcare of Atlanta and from the departments of Human Genetics and Psychiatry and Behavioral Sciences at Emory University. A total of 28 (26.7% of overall sample) individuals with 22qDS ranging in age from 14 to 29 years were included in the current sample. Exclusion criteria for the 22qDS group were a neurological disorder, mental retardation, current substance abuse/addiction, and any Axis I disorder. Thus, the 22qDS group did not include individuals who met Axis I criteria for any psychosis or autistic-spectrum disorder.

Procedure

Diagnostic interviewing. Following the telephone-screening interview, individuals who met criteria for inclusion in the study were invited for an initial four-hour research assessment. All assessments were videotaped and conducted by graduate-level examiners or licensed psychologists. Research staff, including a licensed clinical psychologist and psychiatrist, reviewed videotaped interviews as well as other materials to determine diagnostic status. Each assessment included a battery of diagnostic measures as well as genotyping.

Genotyping. Saliva was collected using the Oragene DNA Kit from DNAGenotek (cat. no. OG-100). DNA was extracted from 800ul of Oragene saliva using the PureLink genomic DNA mini kit (Invitrogen, cat. No. K1820-01). 80-100ul of DNA was collected. The DNA was quantified at the Emory Center for Medical Genomics using pico-green. The DNA was then diluted to a working concentration of 1ng/ul and plated, using the Biomek FX, onto a 384-well microplate. For each sample, 5ul of working DNA was added to an individual well (5ng total) and allowed to dry down overnight. Negative controls and duplicates were incorporated into the DNA plate and the sample order was documented on an excel spreadsheet.

The following day, 5ul of assay mix was added to each DNA well on the 384-well plate using the Biomek FX. The assay mix contained Universal PCR Master Mix no amperase UNG (Applied Biosystems cat. no. 4326614), SNP genotyping assay (specific to each SNP, Applied Biosystems), and dH20. Real time PCR was performed using the Taqman 7900HT and analyzed using SDS version 2.3 software (both, Applied Biosystems). Genotypes were acquired using the allelic discrimination program (SDS version 2.3) for samples with quality values at 95% or greater. The absolute quantification multi-component plots were used to make manual calls for the genotypes as needed. Because there were so few samples used for the genotyping, genotyping was repeated twice in order to get accurate genotype calling. The genotypes from both experiments were compared using a quality check program. Any discordant data were reanalyzed using the real time PCR data. If the data wasn't sufficient to make a clear genotype call (e.g., the reaction signal wasn't robust), the genotypes were considered indeterminable.

Measures

Structured Interview for DSM-IV Personality Disorders (SIDP-IV). The SIDP-IV (Pfohl et al., 1997) is a semi-structured interview that assesses DSM-IV Axis II criteria using questions about relationships, interests and activities, and emotions. Interviewers rate personality disorder criteria on a scale from 0 (not present) to 3 (strongly present). The style of the interview is designed such that it is more difficult to maintain a particular response style because diagnostic

criteria for any given disorder are not necessarily presented together. This measure emphasizes trait functioning, states, moods, or behaviors induced by an external stimulus. The semi-structured interview, taking between 60 and 90 minutes to complete, includes a portion of the measure that allows interviewers to rate clinical observations of each participant. Because of the one-to-one correlation between the SIDP-IV and the DSM-IV criteria, it is assumed to be a valid measure of personality disorders.

The SIDP-IV has been used in various studies as an assessment of personality disorders. Brent and colleagues (1990) administered the SIDP-IV to adolescents and got lower inter-rater reliability than in studies of adults, although there was some modest reliability. SIDP-IV inter-rater reliability in adults for both diagnoses and symptoms is very strong (Rogers, 2001). Like most measures of personality disorders, there is a lack of studies evaluating test-retest reliability (Rogers, 2001). It was assumed to be valid when it was constructed given the one-to-one correlation between the items on SIDP-IV and the DSM-IV diagnostic criteria. Others, however, have investigated the validity of SIDP-IV scales, which are thought to have good construct validity in that they appear to yield comparatively discrete diagnostic categories. Further, when the SIDP-IV was compared to the Personality Disorder Examination (PDE), it yielded much larger Kappa coefficients (Rogers, 2001). The SIDP-IV was used to confirm a personality disorder diagnosis in the SPD group.

Structured Interview for Prodromal Syndromes (SIPS). The SIPS (McGlashan et al., 2001) is a semi-structured diagnostic interview containing a severity scale designed to define and diagnose prodromal states. The SIPS is modeled after the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) and includes 29 items that are organized into four symptom scales: positive, negative, disorganized, and general symptoms. The positive symptom scales include items that assess unusual thought content and delusional ideas, suspiciousness and persecutory ideas, and grandiosity. The negative symptom scales include items measuring social isolation or withdrawal, avolition, decreased expression of emotion, decreased experience of

emotions, decreased ideational richness, and deterioration of role functioning. Disorganized symptom scales include items assessing odd behavior or appearance, bizarre thinking, trouble with focus and attention, and impairment in personal hygiene and social attentiveness. The general symptoms scale includes ratings on sleep disturbance, dysphoric mood, motor disturbances, and impaired tolerance to stress. Rated scores range from 0 to 6, and scores of 0-2 are considered to be non-prodromal. Individuals with scores falling between 3 and 5 are thought to be in the prodromal category, and scores of 6 are in the psychotic category (Miller et al., 1999).

Autism Diagnostic Interview-Revised (ADI-R). The ADI-R (Lord et al., 1994) is a clinical diagnostic instrument that is comprised of 111 items and is designed to assess current and most abnormal level of functioning of autism and autistic signs in adults and children. The instrument consists of five sections, and for the purposes of this study, only selected items were used: questions on social interaction (19 items), communication and language (4 items), and repetitive, stereotyped interests and behaviors (11 items). For each item, the interviewer is required to question the parent / guardian about the child's current level of functioning with respect to the autistic feature and the child's level of functioning during early childhood, age range from birth through toddlerhood. See Appendix A for a description of the ADI-R items.

Within these areas, questions cover verbal and nonverbal communication, social development and play, and interests and behaviors. Although the interview uses a diagnostic algorithm to determine a diagnosis of autism for each participant, the algorithm was not used in the present study since a previous diagnosis of autism would have excluded the participant from the study. It was therefore determined that although many participants would likely display autistic features, it would be unlikely that any of the participants would meet diagnostic criteria for autism.

A trained clinician administered the ADI-R interview to the parent of the adolescent participant, and responses were scored based on the caregiver's description of the adolescent's past and current behavior. For the purposes of the current study, item scores will be utilized

rather than the algorithm. Each item receives a score ranging from 0 to 3, with 0 indicating that the behavior in question is probably present but criteria are not fully met. A score of 2 indicates the presence of definite abnormal behavior, and a score of 3 indicates that the behavior is of extreme severity (Lord et al., 1994). The ADI-R has shown acceptable reliability and validity with various samples, and has been shown to differentiate between children with autism and other children with mental retardation or language impairments (Hill et al., 2001; Lord, Rutter, Storochuk, & Pickles, 1993; Lord et al., 1994; Lord et al., 1997).

Several studies have explored the factor structure of the ADI-R and some of the instrument's items. Tanguay and colleagues (1998) performed a factor analysis on 28 items of the ADI-R that related to social communication and found three main factors in this area of functioning. Cuccaro and colleagues (2003) performed a principle components analysis (PCA) and a factor analysis (FA) on selected items from the section on restricted or repetitive behaviors and interests. From these analyses, they extracted two separate factors that they termed *repetitive motor sensory actions* and *resistance to change*. Tadevosyan-Leyfer and colleagues (2003) selected 98 items that were identical or closely resembled items in the ADI and the ADI-R and performed a PCA that yielded six factors: *spoken language*, *social intent*, *compulsions*, *developmental milestones*, *savant skills*, and *sensory aversions*. Finally, Constantino and colleagues (2004) performed a cluster analysis and a PCA and found the presence of a single, underlying factor in the ADI-R that taps the three domains of autistic disorder: social interaction deficits, communication and language deficits, and restricted and repetitive behaviors and interests.

Data Analysis

Descriptives. Sociodemographic and clinical information about each diagnostic group was determined using basic descriptive (i.e., measures of central tendency and variation for continuous variables) and frequency (i.e., counts for categorical data) analyses in the statistical data analysis program *Statistical Package for the Social Sciences*, version 17.0 (SPSS 17.0). This

included age, sex, race or ethnicity, severity of childhood and current autistic features, severity of prodromal symptoms, and COMT genotype. Analysis of variance (ANOVA) was used to determine sociodemographic differences between the three diagnostic groups and to identify potential covariates for the more complex analyses. Finally, constants were added and transformations (i.e., logarithm and square root) were applied to non-normal, continuous clinical variables to satisfy assumptions of parametric statistical tests. With the exception of the item analyses, the three domains of communication, social interaction, and repetitive interests and behaviors of the ADI-R and the four domains of positive, negative, disorganized, and general symptoms of the SIPS were utilized for all analyses.

Diagnostic group differences. Multivariate Analysis of Covariance (MANCOVA) was used to compare the three diagnostic groups on childhood autistic features, current autistic features, and current prodromal symptoms using sex as an additional independent variable while controlling for age and race. Three MANCOVA analyses were conducted: (1) childhood autistic features in all three domains (communication, social interaction, and repetitive interests and behaviors); (2) current autistic features in all three domains; and (3) current prodromal symptoms in all four domains. To maintain statistical power, planned comparisons based on a priori hypotheses were used to follow up on significant omnibus tests. Additional analyses (i.e., homoscedasticity and multicollinearity) were conducted to ensure that MANCOVA assumptions were met. Finally, partial eta squared (partial η^2) was used as an effect size indicator, with the following conventions used: small = 0.01; medium = 0.06; large = 0.14 (Kittler, Menard & Phillips, 2007).

Correlational analyses. Pearson's product moment correlation *r* was used to examine the relationship between childhood and current autistic features and current prodromal symptoms within the SPD and 22qDS diagnostic groups. An *r*-to-*z* transformation was conducted to convert the *r* correlation for each group (representing the relationship between each set of clinical variables) into a standardized measure, and these standardized correlations were statistically

compared to test for differences between the two diagnostic groups with respect to the strength of the correlations.

Cluster analysis. Hierarchical cluster analysis was used for childhood and current autistic features and current prodromal symptoms to determine possible homogeneous subgroups of cases across the SPD and 22qDS sample (i.e., all participants in each of these groups were combined into one group). Given that each of the variables was continuous, distance between the clusters was determined using the Euclidean distance measure, with the minimum and maximum number of clusters set at two and four, respectively. A within-groups linkage method was used to create the smallest possible distance between all pairs in the resulting clusters. Each cluster resulting from the analysis was then compared on a variety of sociodemographic and clinical characteristics, including diagnostic group (SPD versus 22qDS), autistic features, and prodromal symptoms.

Discriminant function analysis. Discriminant function analysis (DFA) was used to identify optimal weighted combinations of clinical variables that best distinguished the SPD and 22qDS diagnostic groups. All clinical variables were entered as independent variables (i.e., three childhood autistic feature domains, three current autistic feature domains, and four current prodromal symptom domains). The dependent, or grouping variable, was the variable designating the two diagnostic groups (SPD and 22qDS). Independent variables were entered using a stepwise procedure and Wilks' lambda *F*-test was used to determine the significance of the discriminant model. Variables were entered or removed from the analysis based on their ability in differentiating between the two diagnostic groups, and standardized coefficients were examined to qualitatively identify the function(s). Group classification results were examined to determine how well group membership was predicted using the predictor variables. Kappa statistics were also computed to assess the accuracy in prediction of group membership. Finally, correctly- and incorrectly-classified participants in each diagnostic group were compared to one another.

Genotype analysis. The relationship between COMT genotype and each of the autistic feature and prodromal symptom domains was examined using MANCOVA, which allowed for the investigation of main effects of genotype as well as potential interactions between genotype, diagnostic group status, and sex while controlling for age and race. To increase power, full factorial analyses were not carried out given that the main effects of diagnostic group and sex were examined during the overall group differences analyses. Tukey post hoc analyses were used to follow up on significant MANOVA omnibus tests to identify specific significant group comparisons. Additional analyses (i.e., homoscedasticity and multicollinearity) were conducted to ensure that MANOVA assumptions were met. Finally, partial eta squared (partial η^2) was used as an effect size indicator.

Results

Sociodemographic and Clinical Information. Participants were 47 healthy controls, 30 individuals with SPD, and 28 individuals with 22qDS. Descriptive characteristics of the clinical variables as well as sociodemographic information according to diagnostic group are provided in Table 1. As shown, there were 48 (45.7%) females and over half the sample was Caucasian (n = 70, 66.7%). The ages of study participants ranged from 11 to 29 years, with a mean age of 15.5 ± 3.5 years. Genotype data was available for 62 (59.0%) participants (26 controls, 13 SPD participants, and 23 22qDS participants).

Preliminary analyses were conducted to test potential covariates and examine the distributions of the continuous variables to ensure that assumptions of parametric statistical procedures were satisfied. One-way ANOVA showed that the three diagnostic groups differed significantly on age ($F = 39.5$, $p < 0.001$), with 22qDS participants being significantly older than SPD and control participants (no age difference between the control and SPD participants). Chi-square analyses showed significant differences in the proportion of racial groups ($\chi^2 = 22.5$, $p <$

0.01), with a greater proportion of African American participants in the control sample. Subsequent analyses were therefore conducted including age and race as covariates.

There was no significant difference in sex distribution across the three diagnostic groups; however, sex differences were observed for several of the clinical variables. Student's *t*-tests showed that, across groups, males were rated more severely on negative and disorganized prodromal symptoms relative to females. Males also scored more severely on childhood repetitive interests and behaviors, current social interaction, and current repetitive interests and behaviors (Table 2). Sex differences in childhood autistic features, current autistic features, and prodromal symptoms are depicted in Figures 1, 2, and 3, respectively. This pattern of findings is consistent with previous reports of more pronounced negative (Leung & Chue, 2000; Thorup et al., 2007) and autistic (Lingam et al., 2003; Scott, Baron-Cohen, Bolton, & Brayne, 2002) symptoms in males than females. Given these significant differences, sex was included as an independent variable to investigate potential interactions.

Box-plot graphs revealed significant positive skew across all clinical variables, including the three childhood and the three current autistic domains, as well as the four prodromal symptom domains. It is assumed that clinical variables of this nature tend to be positively skewed (i.e., more individuals fall within a normal range of scores, whereas less individuals fall within a more extreme range of scores); thus, a constant was added and a square root transformation was applied to each of the clinical variables to correct for this non-normality and ensure that parametric statistical analyses could be utilized. Box-plots were used to examine these new clinical variables, and results showed that these new variables more closely approximated a normal distribution.

Diagnostic group differences. First, MANCOVA was used to test for diagnostic group and sex differences in childhood autistic features (Table 3). Wilk's Lamda multivariate results supported an overall significant difference among the three diagnostic groups for childhood autistic features ($F = 9.39$, $df = 6, 174$, $p < 0.001$), with a large effect size for the difference

between groups (partial $\eta^2 = 0.25$). There was not a significant main effect of sex nor was there a significant interaction between diagnostic group and sex. Table 3 shows the univariate results, which indicated that childhood communication ($F = 6.75$, $p < 0.01$), childhood social functioning ($F = 13.89$, $p < 0.001$), and childhood repetitive interests and behaviors ($F = 5.92$, $p < 0.01$) significantly differed among the three diagnostic groups. Figures 4 and 5 present clustered bar graphs representing the mean values for each childhood autistic feature variable by diagnostic group and within sex, respectively.

Table 4 presents the results of a priori hypotheses regarding the differences among the three diagnostic groups. Planned comparisons for the domains found to be significant in the univariate analyses were conducted to compare the following groups: (a) 22qDS with control, (b) SPD with control, and (c) 22qDS and SPD. Results showed that for childhood communication, 22qDS participants had more severe scores relative to both control participants ($t = 5.13$, $p < 0.001$) and to SPD participants ($t = 3.59$, $p < 0.01$). For childhood social interaction, 22qDS participants did not differ from control participants, but SPD participants had significantly more severe scores relative to both controls ($t = 5.12$, $p < 0.001$) and 22qDS participants ($t = 3.83$, $p < 0.001$). For childhood repetitive interests and behaviors, 22qDS participants did not differ from control participants, but, again, SPD participants significantly differed from controls ($t = 2.89$, $p < 0.01$) as well as 22qDS participants ($t = 2.17$, $p < 0.05$).

Second, MANCOVA was used to examine differences in the severity of current autistic features between the three diagnostic groups, with sex as an independent variable (Table 5). Multivariate tests showed an overall significant difference among the three diagnostic groups for current autistic features ($F = 8.57$, $df = 6, 184$, $p < 0.001$), with a large effect size for the difference between groups (partial $\eta^2 = 0.22$). There was no significant main effect of sex or significant interaction between diagnostic group and sex. Univariate analyses showed that deficits in current communication ($F = 10.56$, $p < 0.001$), current social interaction ($F = 12.72$, $p < 0.001$), and current repetitive interests and behaviors ($F = 6.43$, $p < 0.01$) significantly differed

among the three groups. Figures 6 and 7 present the mean values for each current autistic feature variable by diagnostic group and within sex, respectively.

Table 6 presents the results of a priori hypotheses regarding the differences among the diagnostic groups. Planned comparisons for the domains found to be significant in the univariate analyses were conducted to compare the following groups: (1) 22qDS with controls, (2) SPD with controls, and (3) 22qDS and SPD. Results showed that 22qDS participants showed more current communication deficits relative to controls ($t = 3.92$, $p < 0.001$) and SPD participants ($t = 3.96$, $p < 0.001$). For current social interaction, 22qDS participants did not differ from control participants, but SPD participants had significantly more severe scores relative to both control participants ($t = 4.00$, $p < 0.001$) and 22qDS participants ($t = 3.58$, $p < 0.01$). For current repetitive interests and behaviors, 22qDS participants did not differ from control participants, but SPD participants again significantly differed from both control participants ($t = 2.86$, $p < 0.01$) and 22qDS participants ($t = 2.49$, $p < 0.05$).

Finally, MANCOVA was used to examine differences in the severity of current prodromal symptoms among the diagnostic groups, with sex as an additional independent variable (Table 7). Multivariate test results supported an overall significant difference among the three diagnostic groups for current prodromal symptoms ($F = 22.11$, $df = 8, 186$, $p < 0.001$), with a large effect size for the difference between groups (partial $\eta^2 = 0.49$). There was also a significant main effect of sex ($F = 7.23$, $df = 4, 93$, $p < 0.001$; partial $\eta^2 = 0.24$), but no significant interaction between diagnostic group and sex.

Univariate analyses revealed that the three diagnostic groups significantly differed on positive prodromal symptoms ($F = 80.03$, $p < 0.001$), negative prodromal symptoms ($F = 37.78$, $p < 0.001$), disorganized prodromal symptoms ($F = 50.63$, $p < 0.001$), and general prodromal symptoms ($F = 32.07$, $p < 0.001$). Univariate analyses also revealed significant sex differences in positive prodromal symptoms ($F = 5.20$, $p < 0.05$), negative prodromal symptoms ($F = 16.27$, $p < 0.001$), and disorganized prodromal symptoms ($F = 20.82$, $p < 0.001$). Figures 8 and 9 present

mean values for each prodromal symptom variable by diagnostic group and within sex, respectively.

Table 8 presents the results of a priori comparisons among the three diagnostic groups. Results showed that for positive symptoms, 22qDS participants showed more severe positive symptoms relative to controls ($t = 7.38$, $p < 0.001$), and SPD participants showed more severe positive symptoms relative to controls ($t = 13.01$, $p < 0.001$) and 22qDS participants ($t = 4.88$, $p < 0.001$). For negative symptoms, 22qDS participants ($t = 9.13$, $p < 0.001$) and SPD participants ($t = 6.09$, $p < 0.001$) scored more severely relative to controls, but 22qDS participants did not differ from SPD participants ($t = 1.27$, p = ns).

For disorganized prodromal symptoms, 22qDS participants ($t = 7.47$, $p < 0.001$) and SPD participants ($t = 7.93$, $p < 0.001$) showed more severe symptomology relative to control participants, but 22qDS participants did not differ significantly from SPD participants in disorganized symptoms ($t = 0.73$, p = ns). Finally, for general prodromal symptoms, 22qDS participants ($t = 7.27$, $p < 0.001$) and SPD participants ($t = 6.32$, $p < 0.001$) showed significantly more severe symptomology, but 22qDS participants again did not differ from SPD participants ($t = 0.92$, p = ns).

Item-by-item analyses. Diagnostic group comparisons were conducted on items within each domain separately by sex. For the childhood autistic features domain, female 22qDS participants scored more severely than female SPD participants on articulation / pronunciation ($t = 6.37$, $p < 0.001$), but female SPD participants scored more severely than female 22qDS participants on inappropriate facial expressions ($t = 2.97$, $p < 0.01$), group play ($t = 2.49$, $p < 0.05$), social disinhibition ($t = 3.40$, $p < 0.01$), and idiosyncratic responses to sensory stimuli ($t = 2.72$, $p < 0.05$). Male SPD participants scored more severely than male 22qDS participants on social smiling ($t = 2.59$, $p < 0.05$), group play ($t = 2.64$, $p < 0.05$), friendships ($t = 2.33$, $p < 0.05$), social disinhibition ($t = 3.28$, $p < 0.01$), and other stereotypies ($t = 2.35$, $p < 0.05$).

Similarly, for the current autistic features domain, female 22qDS participants scored more severely than female SPD participants on articulation / pronunciation ($t = 4.52$, $p < 0.001$) and gait problems ($t = 2.63$, $p < 0.05$), but female SPD participants scored more severely than female 22qDS participants on offering comfort to others ($t = 2.54$, $p < 0.05$), inappropriate facial expressions ($t = 3.42$, $p < 0.01$), social disinhibition ($t = 2.72$, $p < 0.05$), idiosyncratic responses to sensory stimuli ($t = 3.59$, $p < 0.01$), and aggression toward others ($t = 2.89$, $p < 0.05$). Male 22qDS participants scored more severely than male SPD participants on articulation / pronunciation ($t = 2.29$, $p < 0.05$), whereas male SPD participants scored more severely than male 22qDS participants on social smiling ($t = 2.26$, $p < 0.05$), social disinhibition ($t = 3.33$, $p < 0.01$), aggression toward family ($t = 2.38$, $p < 0.05$), aggression toward others ($t = 2.69$, $p < 0.05$), and self-injurious behavior ($t = 2.29$, $p < 0.05$). Thus, for both males and females, the SPD subjects manifested greater deficits than the 22qDS group on items tapping social behavior in childhood and currently.

Finally, for the prodromal symptom domains, female SPD participants scored more severely than female 22qDS participants on unusual thought content ($t = 2.21$, $p < 0.05$), suspiciousness / persecution ($t = 2.22$, $p < 0.05$), perceptual abnormalities ($t = 3.10$, $p < 0.01$), decreased ideational richness ($t = 2.37$, $p < 0.05$), bizarre thinking ($t = 5.25$, $p < 0.001$), and attentional / focus problems ($t = 3.63$, $p < 0.01$). Male SPD participants scored more severely than male 22qDS participants on grandiosity ($t = 2.10$, $p < 0.05$), disorganized communication ($t = 2.78$, $p < 0.05$), and bizarre thinking ($t = 2.09$, $p < 0.05$).

Correlational analyses. Pearson product moment correlation was used to examine relations among childhood autistic features, current autistic features, and prodromal symptoms using one-tailed tests (Table 9). As shown, the results generally suggest modest continuity between childhood and current deficits, as most of the coefficients are positive. But the patterns differ for the two diagnostic groups, and the strength of the associations is greater for the SPD group. Within the SPD sample, all significant coefficients were positive: childhood

communication deficits correlated with negative symptoms, childhood social interaction deficits with general symptoms, current social interaction deficits with general symptoms, childhood and current repetitive interests and behaviors with negative symptoms, and current repetitive interests and behaviors with general symptoms. In contrast, for the 22qDS group, the only significant positive correlation for the childhood ADI measures was between childhood communication deficits and positive prodromal symptoms. There were also positive correlations between current social interaction deficits and negative symptoms, but current communication deficits were inversely correlated with general symptoms.

A Fisher's *r*-to-*z* transformation was conducted, and *z*-tests were used to compare the correlation coefficients across the diagnostic groups. Results showed that the two groups (SPD and 22qDS) differed significantly in the correlations between childhood communication deficits and general symptoms. As noted, the correlation was negative in 22qDS participants but positive in SPD participants (-0.30 versus 0.23). The coefficients for the relationship between childhood social interaction deficits and general symptoms were stronger for SPD than 22qDS participants (0.46 versus -0.07).

Cluster analysis. A hierarchical cluster analysis was performed to identify potential homogeneous syndromal subgroups of participants across the SPD and 22qDS groups ($n = 50$) based on clinical symptoms. The minimum and maximum number of clusters was set at two and four, respectively, and a cluster membership variable was created to classify each participant into a cluster. Euclidean distance measures and a within-group linkage method were used. The cluster analysis was conducted using the three childhood autistic feature domains, the three current autistic feature domains, and the four prodromal symptom domains.

Results indicate an optimal solution of two clusters, with 28 (56.0%) participants in the first cluster, and 22 (44.0%) participants in the second cluster. Participants in the first cluster tended to be older ($t = 1.71$, $p = 0.09$), and scored significantly more severely on childhood and current communication deficits (Figures 10 and 11), and negative and disorganized prodromal

symptoms (Figure 12). The first cluster was also significantly more likely to be comprised of 22qDS participants, whereas the second cluster was significantly more likely to be comprised of SPD participants ($\chi^2 = 13.49$, $p < 0.001$). The two clusters did not differ in sex, race, or COMT genotype distribution. These results are presented in Table 10.

Further analyses were conducted to determine possible differences between the two clusters within each diagnostic group (i.e., why some 22qDS participants clustered differently than other 22qDS participants). The two clusters differed significantly on childhood and current communication deficits and current social interaction problems, with 22qDS individuals in the first cluster ($n = 21$) scoring more severely than 22qDS individuals in the second cluster ($n = 5$). Individuals in the first cluster also scored more severely on positive and negative prodromal symptoms. There were no age, sex, or COMT genotype differences between the two clusters within the 22qDS sample (Table 11).

The same analyses were conducted on SPD participants only. Results showed that within the SPD group, the two clusters differed significantly on childhood and current communication deficits, as well as disorganized prodromal symptoms. The SPD individuals in the first cluster ($n = 7$) scored more severely in these areas than the SPD individuals in the second cluster ($n = 17$). Furthermore, the first cluster within the SPD sample was comprised only of males ($\chi^2 = 7.06$, $p < 0.01$). There were no age, sex, or COMT genotype differences between the two clusters within the SPD sample (Table 11).

Discriminant function analysis. Discriminant function analysis was conducted to determine the optimal combination of symptoms across domains (childhood autistic features, current autistic features, and prodromal symptoms) discriminating between the two diagnostic groups. Wilk's Lamba and chi-square was used to test the significance of each function that emerged from the analysis, and using a stepwise method, all clinical variables were entered as independent variables. Results showed that a weighted combination of positive prodromal

symptoms, general prodromal symptoms, childhood communication deficits, and childhood social interaction deficits best distinguished the two diagnostic groups ($\chi^2 = 55.10$, $p < 0.001$). The canonical correlation for this function shows that 69.8% of the variability of the scores for these variables is accounted for by differences between the two diagnostic groups.

Standardized coefficients for the correlation between each variable and the function (i.e., the unique contribution of each variable to the discriminant function) showed that childhood social interaction deficits and positive symptoms correlated positively to the discriminant function, while childhood communication deficits and general symptoms correlated negatively to the function. The means of each diagnostic group for the function were examined next using group centroids; results showed that the SPD group showed significantly higher scores for the function relative to the 22qDS group. Table 12 shows differences in sociodemographic and clinical variables for the two predicted groups.

Group classification statistics were examined using the predicted group membership variable yielded by the discriminant function analysis. Of the sample of 53 cases, 94.3% were classified correctly. Within each diagnostic group, 96.3% of the 22qDS participants and 92.3% of the SPD participants were correctly classified. A Kappa statistic was used to assess the accuracy of this classification by performing a chi-square analysis of diagnostic group with the predicted group membership variable taking into account chance agreement. Results showed a value of 0.80 ($p < 0.001$), indicating high accuracy in prediction.

To determine possible differences between the 22qDS participants who were correctly classified ($n = 26$) and those who weren't (i.e., classified better as SPD; $n = 1$), the comparison was restricted to 22qDS participants only, and t-tests were used to look for potential differences between these two groups. Results showed only a trend for those who were incorrectly classified to display more severe positive ($t = 1.79$, $p = 0.08$) and general ($t = 1.86$, $p = 0.07$) prodromal symptoms. The two groups did not differ with respect to sex or age. The data file was then restricted to SPD participants only, in order to look for differences between correctly-classified

SPD participants (n = 24) and incorrectly-classified SPD participants (i.e., classified better as 22qDS; n = 2). Results showed that those SPD participants who were incorrectly classified scored significantly more severely on current communication deficits than correctly-classified SPD participants (t = 3.71, $p < 0.01$). Results are shown in Table 13.

Genotype analysis. Potential effects of COMT genotype were first examined among those participants having two COMT alleles (i.e., control and SPD participants). MANCOVA was used to examine both the main effects of COMT genotype (Val/Val, Val/Met, or Met/Met), as well as possible interactions between COMT, diagnostic status (control vs. SPD) and sex on autistic features and prodromal symptoms. For both childhood (Table 14) and current (Table 15) autistic features in control and SPD participants, results showed no main effect of COMT genotype and no significant interactions between COMT genotype, diagnostic group status, or sex.

For prodromal symptoms, MANCOVA results showed significant main effects for COMT genotype (F = 2.61, df = 8, 48, $p < 0.05$; partial $\eta^2 = 0.30$); however, follow-up univariate results, presented in Table 16, showed only a trend for disorganized prodromal symptoms to significantly differ among the three COMT genotypes (F = 3.31, p = 0.05) and post-hoc analyses were non-significant. Multivariate tests also showed a significant interaction between COMT genotype and diagnostic group status (F = 5.76, df = 12, 63.79, $p < 0.001$; partial $\eta^2 = 0.48$). Univariate results revealed that the interaction was significant for all prodromal symptoms. Thus, follow-up multivariate tests were conducted within each diagnostic group to examine symptom differences between the three COMT genotype groups. Results showed that in the control sample, prodromal symptom severity in any domain did not differ between the three COMT groups. However, in the SPD sample, multivariate results showed a significant main effect of genotype (F = 3.48, df = 8, 12, $p < 0.05$) and univariate results were significant for disorganized symptoms. Post-hoc analyses indicated that the Met/Met genotype (μ = 2.03, SD = 0.22) showed

significantly more severe disorganized symptoms relative to both the Val/Met ($\mu = 1.43$, SD = 0.17) and Val/Val genotypes ($\mu = 1.45$, SD = 0.31); this is presented in Figure 16.

To allow for comparisons between SPD and 22qDS participants with respect to potential effects of COMT genotype, heterozygous SPD participants were excluded. Thus, 22qDS Val carriers and SPD Val/Val genotype were classified as Val carriers, whereas 22qDS Met carriers and SPD Met/Met genotype were classified as Met carriers. MANCOVA was used to examine main effects of diagnostic group status (22qDS vs. SPD) and COMT genotype (Val vs. Met), as well as possible interactions between diagnostic group status and COMT genotype on autistic features and prodromal symptoms. Results for both childhood (Table 17) and current (Table 18) autistic features revealed no significant main effects and no significant interactions.

For prodromal symptoms, there was no main effect of COMT genotype; however, results revealed a significant interaction between COMT genotype and diagnostic group status ($F = 2.22$, $df = 8, 36$, $p = 0.04$), with a large effect size (partial $\eta^2 = 0.33$). Univariate analyses, presented in Table 19, showed that the interaction was significant for general symptoms ($F = 5.39$, $p < 0.05$), and a trend for significance for positive ($F = 2.98$, $p = 0.07$) and disorganized ($F = 3.28$, $p = 0.06$) symptoms. Follow-up comparisons showed that within the 22qDS sample, Val carriers did not differ from Met carriers in any prodromal symptom domain. However, in the SPD sample, Met carriers ($\mu = 1.90$, SD = 0.14) showed significantly more severe general symptoms relative to Val carriers ($\mu = 1.35$, SD = 0.11; $t = 5.01$, $p < 0.05$). This is shown in Figure 16.

The interaction was also investigated within genotype (Val versus Met carriers) across diagnostic groups. Among Val carriers, 22qDS participants showed significantly more severe general prodromal symptoms than SPD participants ($\mu = 1.77$, SD = 0.31 versus $\mu = 1.35$, SD = 0.11; $t = 2.24$, $p < 0.05$). This is shown in Figure 17. Among the Met carriers, SPD participants showed significantly more severe positive ($\mu = 1.99$, SD = 0.21 versus $\mu = 1.56$, SD = 0.18; $t =$

3.10, $p < 0.01$) and disorganized symptoms ($\mu = 2.03$, SD = 0.22 versus $\mu = 1.49$, SD = 0.22; $t = 3.15$, $p < 0.01$). These results are illustrated in Figures 18 and 19, respectively.

Discussion

Recent genetic studies have demonstrated that autistic- and schizophrenia-spectrum disorders are associated with copy number variations and microdeletions in the same chromosomal regions (Burbach & van der Zwaag, 2009; Guilmatre et al., 2009), suggesting that the two disorders share genetic etiologic factors (Figure 20). Other studies have revealed overlap in the clinical phenomenology of these spectra (Konstantareas & Hewitt, 2001; Nylander & Gillberg, 2001; Petty et al., 1984; Sheitman et al., 2004). The present study examined prodromal symptoms and autistic features in samples of SPD adolescents and individuals with 22qDS, using a sample of healthy controls for comparison purposes. Both of these diagnostic groups show an increased risk of psychotic disorders as well as an elevated incidence of autistic-like behaviors or autistic-spectrum disorders. Comparing these two groups has the potential to shed light on the nature and origins of these overlapping syndromes. The general pattern of results indicates that individuals with SPD show more social and stereotypic autistic-related deficits as well as more severe positive prodromal symptoms, while SPD and 22qDS individuals do not differ in negative, disorganized, and general prodromal symptoms.

Autistic features in SPD versus 22qDS: How do they differ?

The first aim of the present study was to contrast the two diagnostic groups with respect to both childhood and current autistic features. As described above, previous research has demonstrated that individuals diagnosed with SPD manifest a greater severity of autistic-like behaviors relative to individuals with other personality disorders and healthy individuals (Esterberg et al., 2009), and others have found that schizotypal symptoms, or schizotypy, is positively correlated with features of Asperger's disorder in healthy controls (Hurst et al., 2007). Furthermore, individuals with schizophrenia have been found to show features of autistic-spectrum disorders at a greater prevalence than individuals with other psychiatric disorders and

healthy control subjects (Havelcova, 1968; Konstantareas & Hewitt, 2001; Nylander & Gillberg, 2001; Petty et al., 1984; Reiser & Brown, 1964; Sheitman et al., 2004). However, while features of autism have been found to be more common in schizophrenia than in controls, findings suggest that individuals with schizophrenia are at no greater risk for developing the disorder of autism than individuals in the general population (Volkmar & Cohen, 1991).

However, research suggests that individuals with 22qDS are at greater risk for exhibiting autistic features as well as developing autistic-spectrum disorders relative to healthy controls. Niklasson and colleagues (2009) suggest that autistic-spectrum disorders should be considered to be main elements in the behavioral phenotype of children with 22qDS. Vorstman et al. (2006) found that 50% of 22qDS child patients were diagnosed with an autistic-spectrum disorder, while Antshel and colleagues (2007) found that 41% of their sample of children and adolescents with 22qDS met criteria for an autistic-spectrum disorder and 94% of these individuals were diagnosed with a co-occurring psychiatric disorder. Other studies have shown similar results (Fine et al., 2005; Niklasson et al., 2001). Given these findings, it was hypothesized that 22qDS individuals would display the most severe autistic features in all three domains. Further, it was hypothesized that SPD individuals would show an intermediate level of autistic features, with control participants showing the lowest severity of symptoms.

Interestingly, this hypothesis was only partially confirmed. Individuals with 22qDS only showed significantly more severe autistic features in the domain of communication, relative to both SPD and control participants. This was observed for both childhood and current communication deficits. This finding could be partially attributable to the mouth and palate malformations (i.e., articulation and pronunciation), which are common in individuals with 22qDS and impair communication. Contrary to prediction, it was the SPD participants who showed the greatest severity on the other two ADI-R domains: social interaction and repetitive interests and behaviors. In contrast, the 22qDS group did not significantly differ from the healthy control participants on these two scales. To more closely examine each domain of

functioning, an item-by-item analysis was conducted by sex, given the higher prevalence of autistic symptoms in males. For both males and females, the results generally parallel those observed for the overall diagnostic group comparisons, in that the items that most distinguish the SPD and 22qDS groups primarily fall within the social interaction domain.

The more pronounced level of social deficits in the SPD group, as measured by the ADI-R, is noteworthy in light of the documented higher risk for autistic-spectrum in 22qDS patients. It is particularly remarkable that individuals in the SPD group were rated by parents as showing more severe *childhood* social impairments and repetitive interests and behaviors than individuals in the 22qDS group. As discussed below, the two diagnostic groups were similar in their severity of current prodromal symptoms, with the exception of positive symptoms, in which the SPD group scored higher. This is to be expected, given that perceptual and ideational abnormalities are among the defining features of SPD.

There are several potential explanations for the pattern of group differences in childhood and current scores on the ADI-R. First, and perhaps most compelling, it is likely that the exclusion of subjects with Axis I disorders from the present study obscured the diagnostic group differences, because the 22qDS patients most likely to have pronounced impairment scores on the ADI-R social and repetitive behavior items were excluded. This would account for the absence of statistically significant differences between the 22qDS group and the healthy controls on these scales. But this does not explain the elevated ADI-R scores for the SPD group relative to both the 22qDS and healthy control groups. These diagnostic group differences indicate that the ADI-R is tapping into some childhood behavioral deficits that are more common in SPD youth. Further, it may be that these behavioral features differ from those the ADI-R is measuring in the 22qDS sample.

The results of the correlational analyses shed light on this possibility. Another aim of the study was to examine relationships among autistic features and prodromal symptoms. Research on the relationships between autistic features and symptoms of schizophrenia is limited, and

studies of autistic features and prodromal symptoms are nonexistent. Sheitman and colleagues (2004) first studied the continuous relationship between autistic features and symptoms of schizophrenia in a sample of patients with treatment-resistant schizophrenia. They found that autistic features were present in these patients and that they tended to correlate with negative symptoms. Given phenomenological similarities between autistic features and the negative symptoms of schizophrenia, these findings were not surprising. Hurst et al. (2007) was the first to study the relationship between symptoms on the milder ends of the autistic and schizophrenia spectrums, and they showed that more severe Asperger's traits were moderately correlated with more severe schizotypy scores. Finally, in a previous study including the current SPD and healthy control samples as well as adolescents with other personality disorders, Esterberg and colleagues (2009) found that childhood and current autistic features predicted 26% and 28% of the variance in total schizotypal symptoms, respectively. Similar results were found for the relationship between autistic features and positive, negative, and general prodromal symptoms.

Based on previous findings, it was hypothesized that prodromal symptoms would be positively correlated with autistic features, and that this relationship would be strongest between social interaction deficits and negative symptoms. Similar to what was found by Hurst et al. (2007), communication deficits were correlated with positive symptoms, but only in the 22qDS sample. Also in line with past research and the current study's hypotheses was the relationship between current social interaction deficits and negative symptoms. Although it was expected that disorganized and general prodromal symptoms would correlate with autistic features, it was thought that the relationship would be less strong. However, autistic features did not correlate at all with disorganized symptoms, and they were actually negatively correlated with general symptoms.

The SPD sample showed different significant relationships. Childhood communication deficits correlated with more severe general symptoms, childhood social interaction deficits correlated with more severe negative symptoms, and current social interaction deficits correlated

with more severe general symptoms. Furthermore, childhood and current repetitive interests and behaviors correlated with more severe negative symptoms, and current repetitive interests and behaviors correlated with more severe general symptoms. Autistic features did not correlate with positive or disorganized prodromal symptoms.

Of most interest was that the relationship between childhood communication deficits and general symptoms was significantly different between SPD and 22qDS participants. In 22qDS participants, communication deficits were related to less general symptoms, whereas in SPD participants these deficits were related to more general symptoms. As stated above, general symptoms include such symptoms as sleep disturbance, dysphoric mood, motor disturbance, and impaired tolerance to normal stress. It is not clear why the relationship was negative in 22qDS but positive in SPD; it could be that greater communication deficits lead to difficulties in communicating sleep, mood, and stress difficulties for individuals with 22qDS individuals. Nonetheless, this finding should be interpreted with caution given that neither of the coefficients representing these individual relationships was statistically significant.

Interestingly, the relationship between childhood social interaction deficits and general symptoms was significantly stronger in SPD participants relative to 22qDS participants. This finding might be explained statistically by the greater range of social interaction deficits seen in the SPD sample; namely, the more severe social interaction deficits evident in the SPD participants led to a greater chance in detecting a significantly stronger relationship. However, social interaction deficits were differentially related to any other prodromal symptom domain, lending some support to the hypothesis that there is a special or unique relationship between autistic-social deficits and general prodromal symptoms in individuals with SPD.

Also of relevance was the relationship between childhood autistic features and current prodromal symptoms: namely, it is only for the SPD group that significant positive correlations are observed between childhood impairment and current negative and general symptoms. Thus, despite the fact that the two diagnostic groups are comparable with respect to current severity of

negative, disorganized and general prodromal symptoms, continuity between childhood deficits and current prodromal symptoms is only observed for the SPD group.

An explanation for this finding may involve the pathogenic processes associated with 22qDS. It has been shown that there is significant developmental change over time in the behavioral deficits associated with 22qDS. Although early cognitive and motor delays are common in 22qDS, the onset of mood and psychotic syndromes is typically in late adolescence and early adulthood. Thus, it appears that the modal risk period for onset of psychotic disorders, especially schizophrenia is similar for 22qDS and non22qDS populations (Bassett et al., 1998; Bassett et al., 2003). However, there is recently accumulating evidence that developmental discontinuities are more pronounced for 22qDS than the general population and other groups at risk for psychosis (Niklasson & Gillberg, 2010). For example, a recent study of a large sample of 22qDs (n=100) subjects revealed a highly significant inverse correlation between age and cognitive function, indicating that 22qDS subjects manifest a pronounced decline ($p < 0.001$) between ages 1 and 35 years (Niklasson & Gillberg, 2010). This was especially the case for processing speed ($p < 0.001$).

Consistent with this, another recent study revealed that 22qDS subjects showed significantly more age-related decline in brain volume; preadolescent 22qDS patients showed larger prefrontal thickness than age-matched controls, whereas older adolescent 22qDS subjects showed more dramatic loss in cortical thickness (Schaer et al., 2009). Furthermore, Shashi et al. (2010) demonstrated that children with 22q11DS show volumetric reductions in gray matter in the frontal cortices, the cingulate gyrus, and the cerebellum; these reductions were related to poorer executive functioning performance. There is no comparable evidence of pronounced developmental decline in cognitive abilities or brain structure in SPD patients. Although some meta-analyses suggest a subtle decline in cognitive function and gray matter volume prior to the onset of psychosis in non-22qDS samples, the change is not consistently observed.

In sum, the limited associations between childhood deficits, especially social impairment, and current prodromal symptoms in the 22qDS group may reflect the greater developmental discontinuity characteristic of this disorder. While the source of this discontinuity is unknown, it has been suggested that developmental changes in gene expression are modifying the phenotype of 22qDS with age (Amati et al., 2007). In other words, the genes affected by the 22q deletion may differ in the timing of their expression such that the phenotypes manifested in patients are characterized by greater developmental variability than that observed in the SPD group. This issue will be discussed again later in connection with syndromal subtypes.

Distinguishing psychosis risk groups on prodromal symptoms

The second aim of the present study focused on similarities and differences in prodromal symptoms between SPD and 22qDS individuals. The prodrome, or the time period directly preceding the onset of a psychotic disorder, is characterized by subthreshold psychotic symptoms, termed prodromal symptoms. SPD is of interest to the prodrome because the disorder is thought to be a more common expression of the underlying diathesis to psychosis (Walker & Diforio, 1997), and SPD symptomology is quite similar to the prodromal symptoms of schizophrenia. Furthermore, research has demonstrated that up to 45% of those with SPD during adolescence go on to develop a psychotic disorder (Miller et al., 2002; Yung et al., 2003). Finally, the presence of SPD during adolescence is now considered to be a prodromal risk syndrome by researchers in the area of schizophrenia.

A recent study published by the one of the largest psychosis-risk groups in the world identified and clinically described several risk groups in an attempt to validate a "prodromal risk syndrome" (Woods et al., 2009). One or more of three criteria were required to be included in the risk syndrome group: new onset or recent worsening of positive symptoms, brief periods of psychotic symptoms, or deterioration in functioning with a diagnosis of SPD/relative with psychosis. While the authors note that the prodrome and SPD can be delineated (i.e., prodrome is defined by progression of illness, whereas SPD individuals can be "stably ill"), the two

syndromes can be comorbid. In the Woods et al. (2009) study, 26% of prodromal subjects met criteria for SPD, while 67% of SPD subjects met criteria for the prodromal risk syndrome. Furthermore, prodromal patients and SPD patients were indistinguishable from prodromal subjects on positive, negative, and general prodromal symptoms on the SIPS. Thus, there is strong evidence that SPD can be considered as a prodromal risk syndrome for psychosis (Woods et al., 2009).

As discussed above, 22qDS is also of interest with respect to prodromal symptoms, given that many researchers have shown that individuals with this genetic disorder are at heightened risk for developing psychotic disorders. Some have demonstrated that psychosis is just as common as autistic-spectrum disorders, while others have suggested that schizophrenia is the most prevalent psychiatric disorder in these individuals (Bassett et al., 2005; Gothelf et al., 2007; Murphy et al., 1999). Psychotic disorders have even been found to be highly prevalent in children and adolescents with 22qDS (Debbane et al., 2006).

Given that both SPD and 22qDS have been shown to be risk syndromes for psychotic disorders, it was hypothesized that individuals with either disorder would show greater severity of prodromal symptoms relative to healthy control participants. The present results are generally consistent with this hypothesis in that SPD and 22qDS participants showed more severe symptoms in all prodromal symptom domains relative to control participants, yet they did not differ from one another in the severity of negative, disorganized, or general prodromal symptoms. Furthermore, an item-by-item analysis showed that the two diagnostic groups were remarkably similar across items in the three domains; the only differences in emerge between SPD and 22qDS participants were ideational richness and attention problems (females only), and bizarre thinking (females and males). These findings are in line with the present study's hypothesis regarding similarities in severity.

The two groups did differ, however, on positive prodromal symptoms, which map onto the positive symptoms of schizophrenia, including hallucinations, delusions, and disorganization.

The differences were seen in each individual item of the positive symptom domain; unusual thought content, suspiciousness, and perceptual abnormalities differed between female SPD participants and female 22qDS participants, while grandiosity and disorganized communication differed between male SPD and male 22qDS participants.

The difference in positive symptoms between the two groups can possibly be attributed to several factors. The first is the differences in recruitment strategies for the two samples. As stated above, the SPD sample was recruited based on the presence of positive signs such as "perceptual difficulties," "odd beliefs," and "trouble communicating." The 22qDS sample was identified solely on the basis of their genetic abnormality. Thus, sample selection procedures could explain the differences in positive symptoms. Alternatively, it is possible that the present SPD sample is at greater risk for psychosis relative to the 22qDS sample. The SPD sample has been studied over a five-year period and approximately 28% of these adolescents with SPD went on to develop a psychotic disorder at some point during the five-year follow-up period. The 22qDS sample, however, has not been followed up, so the percentage of the sample that has gone on to develop a psychotic disorder is not yet known.

Finally, although there is a dearth of research on comparing symptoms in schizophrenia patients with and without 22qDS, it is possible that the present findings reflect a unique prodromal symptom profile in 22qDS. Thus, 22qDs prodromal subjects may show less pronounced positive symptoms. To date, however, the limited research on diagnosed patients with schizophrenia provides no support for this. Bassett and colleagues (2003) compared 22qDS-schizophrenia to schizophrenia without the 22qDS subtype, and found that individuals in the two groups did not differ on positive or negative symptoms of schizophrenia. Murphy et al. (1999) compared non-22qDS schizophrenia to a 22qDS with schizophrenia group, and found no differences in positive symptoms, but more severe negative symptoms in the non-22qDS group.

However, the only study to date on prodromal symptoms in adolescents with 22qDS demonstrated that greater percentages of adolescents show more severe negative, disorganized,

and general prodromal symptoms relative to positive prodromal symptoms (Stoddard et al., 2010). Furthermore, the results herein suggest that SPD and 22qDS as risk groups for psychosis are more similar than different with respect to prodromal symptoms.

Empirical approaches to identifying and differentiating subgroups: Cluster and discriminant function analyses

Another goal of the present study was to investigate the possibility of syndromal subgroups in the SPD and 22qDS samples. Across the two risk groups, two clusters emerged, and these roughly corresponded to the modal syndromes observed within the SPD and 22qDS groups. The first cluster presented more severely on childhood and current communication deficits, and negative and disorganized prodromal symptoms. The first cluster also tended to be older, and was comprised of significantly more 22qDS participants and fewer SPD participants than the second cluster. These results lend support to the notion that the relations between childhood autistic spectrum features and prodromal symptoms differ for the two diagnostic groups. Also of interest were the individuals within each diagnostic group that clustered differently than others with the same diagnosis. This suggests that empirical methods of classifying psychosis risk subgroups should include both prodromal symptoms and childhood autistic features. Future research using larger samples may yield clusters that are differentially associated with conversion to psychosis.

Paralleling the results of the cluster analysis, the discriminant function analysis demonstrated that SPD participants could be discriminated from 22qDS participants on the basis of a weighted combination of positive and general prodromal symptoms, as well as childhood communication and social interaction deficits. Furthermore, the combination of these variables explained the majority of the variance in the difference between the two risk groups. Similar to the cluster analysis, these results suggested that on the basis of this combination of autistic and prodromal variables, some SPD subjects were better classified as 22qDS participants, and vice versa. Nonetheless, using these predictors, over 90% of the subjects were correctly classified. Of

those who were incorrectly classified, more severe prodromal symptoms were related to incorrect classification of 22qDS subjects, and more severe autistic-communication deficits were related to incorrect classification of SPD subjects.

COMT and autistic and prodromal symptoms

The final objective of the current study was to examine the influence of the COMT Val^{158}Met polymorphism on autistic features and prodromal symptoms. COMT is of interest in the study of psychiatric disorders because of its involvement in brain function, particularly in the prefrontal cortex (Tunbridge et al., 2007). The COMT gene encodes for an enzyme that is involved in the age-related breakdown of dopamine, particularly in the prefrontal cortex (Craddock, Owen, & O'Donovan, 2006), and is of particular interest because dopamine is assumed to play a role in the pathophysiology of psychosis. COMT is located within the deletion region of 22qDS, and some researchers hypothesize a link between hemizygosity of COMT (i.e., less breakdown of dopamine) and increased risk for psychosis. Dopamine has also been hypothesized to be involved in autism, particularly with respect to social functioning (Neuhaus, Beauchaine, & Bernier, 2010), lending some support to potential involvement of COMT in the severity of autistic-like features or behaviors.

Results from the current study show no relation between COMT and the severity of either childhood or current autistic features. However, there was a significant association with prodromal symptoms; individuals with SPD who are homozygous Met for COMT show significantly more severe disorganized prodromal symptoms relative to homozygous Val and heterozygous SPD individuals. COMT genotype was not linked with other prodromal symptom dimensions in the SPD sample. These findings converge with some recent studies that have found a relationship between the COMT Met allele and disorganized schizotypal traits (Ma et al., 2007; Sheldrick et al., 2008). However, as reviewed above, other studies indicate that it is the Val allele that is associated with schizotypy (Avramopoulos et al., 2002; Schurhoff et al., 2007),

while others have found no relationship between COMT and schizotypal symptoms (Ishii et al., 2007; Kim et al., 2006).

Discrepancies among the findings suggest that either the significant reported results are chance findings, or that the relation of COMT genotype with psychosis-spectrum symptoms is highly complex. For example, subject characteristics, such as sex, age, and medication status may moderate the relation between COMT genotype and symptoms. Regarding the lack of significant findings in the healthy control sample herein, previous studies may have sampled a broader range of the general population, yielding a wider range of schizotypal symptoms and thus a greater chance of detecting a relationship. Regarding the significant findings in the SPD sample and the null or converse findings in previous schizotypy studies, the present study focused on adolescents with a mean age of approximately 14 years. Given maturational changes in dopamine expression, especially in the prefrontal cortex, the younger age of the present sample seems especially salient and may explain discrepant findings.

Also of interest was that COMT genotype interacted with diagnostic group status in predicting prodromal symptoms. When genotype *and* diagnostic group status are taken into account, Val was the risk allele for 22qDS participants while Met was the risk allele for SPD participants. Thus, COMT genotype was related to previously undetected group differences. Although most previous research has suggested that hemizygosity of the COMT allele does not exert an effect on susceptibility to schizophrenia (Basset et al., 2007) or symptom severity (Murphy et al., 1999; Bassett et al., 2007; Baker et al., 2005) in individuals with 22qDS. Only one study has examined the relationship between COMT and psychiatric problems in adolescents (Bearden et al., 2005). Bearden and colleagues (2005) found that Val hemizygosity was associated with parental report of more severe internalizing and externalizing problems in children with 22qDS.

In summary, the findings of the present study seem to only add to the mixed literature on the influence of COMT on psychiatric disorder susceptibility and symptomology, and further,

they do not shed light on the origins of the inconsistent literature on COMT and autistic or prodromal symptoms. As Craddock, Owen, and O'Donovan (2006) suggest, a clear and consistent relationship between COMT and psychiatric phenotypes has proven to be elusive, and this likely reflects the complexity and subtle effects of risk-related genes.

Limitations and future directions

The present study was limited by a modest sample size and a cross-sectional design. Future studies should focus on longitudinal studies of these two risk groups. The current SPD sample was part of a longitudinal study, and conversion to psychosis could be examined. It would be beneficial to examine this phenomenon in 22qDS individuals as well, and to determine if the progression of symptoms and conversion process was different between the two risk groups. Furthermore, changes in the relationship between autistic features and prodromal symptoms could also be examined, which could provide more insight into etiologic factors. While autistic features have not been found to predict conversion to psychosis (Esterberg et al., 2009), studying this relationship over time using more advanced statistical modeling procedures would be informative.

Lack of age- and sex-matching is potentially another limitation of the study. Previous studies comparing non-22qDS-schizophrenia with 22qDS-schizophrenia have employed age- and sex-matching methods to ensure that appropriate comparisons are being made. The two diagnostic groups in the present study did not differ with respect to sex, but the 22qDS sample was significantly older. While the present study used statistical control for age, future studies should attempt to employ more rigorous methods of matching to ensure that similarities or differences between risk groups are not due to sociodemographic differences such as age, sex, or race/ethnicity.

Finally, future studies should employ larger sample sizes in order to increase the power for predicting conversion to psychosis. The current study's sample size was small, especially with respect to examining the effects of COMT genotype on symptoms. Furthermore, the

current findings, as well as results from prior research, suggest that variation in psychiatric phenotypes is less related to single-gene effects and more related to more complex genetic interactions as well as mutations. As discussed above, the future of this field may lie in genome-wide association and linkage studies; many in this area are beginning to make progress in investigating genetic variants that confer risk for both schizophrenia and autism.

Conclusions

The present study examined autistic features and prodromal symptoms in two groups, both of which show increased risk for both autistic-like behaviors and conversion to psychosis. Despite limitations, the study provides the evidence that the two groups can be differentiated on the basis on several dimensions of childhood autistic features, as well as positive prodromal symptoms. Further, the two groups manifest different relationships between childhood autistic features and prodromal symptoms. Autism and schizophrenia have been shown to overlap phenomenologically, and to share some etiologic factors. It was hypothesized earlier (Esterberg et al., 2009) that the disorders overlap because of susceptibility genes for either disorder being distinct but located within the same region, highlighting the potential relevance of linkage disequilibrium. Thus, continued studies of risk for either disorder in individuals such as 22qDS and SPD, who potentially possess or lack these genes, are of chief importance.

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Appendix A

Definitions of ADI-R Items

Communication / Language

Use of others' bodies to communicate

Abnormal use of another person as a kind of extension of the subject's arm or body. For example, the use of another person's hand to point touch an object, or perform a task such as turning a door knob to open a door, unscrewing a bottle top or lid, or manipulating a zipper or buttons. This behavior will probably take place without any prior attempt to communicate the need or request using sounds or gesture. The physical contact is not to initiate a social approach but rather to facilitate the completion of the task.

Articulation / pronunciation

Refers to the enunciation of the sounds of language.

Social Development and Play

Social smiling

Spontaneous smiling directed at a variety of people, including smiling back at someone smiling at him / her, smiling during an approach, and in response to what someone does or says to him / her.

Showing and directing attention

How and why the subject directs others' attention to toys or objects in which he / she is interested. Focus is on spontaneous directing of attention purely to share interest.

Offering to share

Concerns unprompted, non-routine offers to share a range of different objects with other people.

Sharing enjoyment with others

Attempt to share his / her enjoyment of things that give him / her pleasure with others, with no apparent motive but sharing.

Sharing others' pleasure and excitement

Ability to respond to others' pleasure and excitement; whether or not subject shares the pleasant feelings and joins in the excitement or playfulness.

Offers comfort

Spontaneous unprompted gesture, touch, vocalization, or offer of an object and change in facial expression directed to someone who is sad, ill, or hurt in an attempt to help him / her feel better.

Coming for comfort

Whether the subject seeks comfort if he / she is hurt with a minor injury. Emphasis is on what the subject does on his / her own, before anyone may be aware that he / she is hurt.

Quality of social overtures

Quality of social intentionality when seeking help (not the number of contexts in which such approaches occur). Subject consistently makes vocalizations that are integrate with other behaviors, including eye gaze.

Range of facial expressions

Focus on facial expressions used to communicate, not just those associated with the experience of emotions. A normal range of emotions would be expected to include several more subtle facial expressions used communicatively, including surprise, guilt, disgust, interest, amusement, and embarrassment.

Inappropriate facial expressions

Those expressions that indicate emotions that are incongruent with the situation, such as laughing when someone is upset or hurt or laughing or crying for no discernable reason.

Affection

Spontaneous positive expression of love or caring directed to a specific person and shown through touching, seeking proximity, offers of gifts or vocalization accompanied by an appropriate facial expression.

Social disinhibition

Behavior that is not appropriately modulated according to social expectations in the child's socio-cultural environment. Such disinhibition may arise from a variety of causes, but the aim here is inhibition that arises from a lack of awareness of social cues.

Appropriateness of social responses

How child responds when adults, other than parents attempt to interact with him/her in everyday but non-routine situations.

Social anxiety

Marked anxiety in ordinary social situations, of a degree that is associated with avoidance behavior in the situation

Secure base

Use of caregivers as a base from which he/she can explore. Consider the subject's awareness of the caregiver's location and attention to it, as evidenced by seeking proximity and checking back, and the subject's ability to then go on to interact or explore in a new situation.

Separation anxiety

Overt expression of distress upon separation an pleasure upon reunion typically seen in infants and toddlers.

Group play with peers

Subject's participation in groups of other children in spontaneous games or activities. Co-operation must involve the subject attending to his/her peers and modifying his/her behavior in a way that clearly demonstrates spontaneous, flexible, interactive play.

Friendships

Selective, reciprocal relationships between two persons of approximately the same age who seek each other's company and share activities and interests.

Unusual Interests and Behaviors

Circumscribed interests

A pursuit that differs from ordinary hobbies in its intensity, its circumscribed nature, its non-social quality, and its relative non-progression or development over time. It differs from an unusual preoccupation in that it lacks peculiar or odd content. Circumscribed interests are unusual in their qualities by not in their content.

Unusual preoccupations

An interest that is odd or peculiar in quality, that is unusual in its intensity and lack of social features, and which is repetitive or stereotyped in one or more of its features or elements.

Difficulties with changes in routine or environment

Marked, extreme reactions to a variety of minor changes in how or where or when the subject carries out daily activities. These changes must be minor. Not included would be moving houses or changing schools or a major transition that would be expected to affect any subject. The emphasis for this item is on an unusual degree of upset and/or insistence on maintaining the original condition if a minor aspect of the subject's routine is changed.

Resistance to change

Concerns the subject's marked difficulty wit minor or trivial changes in aspects of the environment that have no direct effect on him/her. For example, the position of ornaments, the orientation of the telephone, clothes worn by people other than the subject. The emphasis is on the subject's unusual negative reaction to these trivial changes that do not have direct bearing on the subject.

Compulsions / rituals

Fixed sequences that are performed as if the subject feels pressure to complete them in a particular order. Compulsions may also include having to place particular objects in exact positions or relationships in space, such as opening all doors at a certain angle or turning all lights off. A compulsion with lights differs from repetitive use of objects scored above in that subject insists that several lights must remain off, rather than carry out a repetitive action of turning lights off and on. Rituals differ from difficulties with changes as described below in that they have sequence and because the subject is imposing an order on events, rather than responding to a perceived change.

Table 1. *Sociodemographic and clinical characteristics*

Variable		Entire Sample (n = 105)	Control (n = 47)	22qDS (n = 28)	SPD (n = 30)
Age (Mean ± SD)*		15.5 ± 3.5	14.0 ± 1.9	19.3 ± 4.1	14.2 ± 1.7
Sex (n, %)	Female	48 (45.7%)	20 (42.6%)	17 (60.7%)	11 (36.7%)
	Male	57 (54.3%)	27 (57.4%)	11 (39.3%)	19 (63.3%)
Race (n, %)*	Caucasian	70 (66.7%)	24 (51.1%)	22 (78.6%)	24 (80.0%)
	African American	29 (27.6%)	22 (46.8%)	3 (10.7%)	4 (13.3%)
	Asian American	2 (1.9%)	0 (0.0%)	1 (3.6%)	1 (3.3%)
	Other	2 (1.9%)	1 (2.1%)	0 (0.0%)	1 (3.3%)
	Hispanic	2 (1.9%)	0 (0.0%)	2 (7.1%)	0 (0.0%)
COMT (n, %)**	Val/Val	13 (33.3%)	10 (38.5%)	11 (47.8%)	3 (23.1%)
	Val/Met	21 (53.8%)	13 (50.0%)	--	8 (61.5%)
	Met/Met	5 (12.8%)	3 (11.5%)	12 (52.2%)	2 (15.4%)
SIPS Positive Symptoms (Mean ± SD)		1.3 ± 0.9	0.5 ± 0.6	1.5 ± 0.6	2.3 ± 0.6
SIPS Negative Symptoms (Mean ± SD)		1.3 ± 1.0	0.5 ± 0.6	2.0 ± 0.8	1.7 ± 0.9
SIPS Disorganized Symptoms (Mean ± SD)		1.0 ± 0.9	0.3 ± 0.4	1.5 ± 0.8	1.7 ± 0.9
SIPS General Symptoms (Mean ± SD)		1.1 ± 1.0	0.4 ± 0.5	1.8 ± 0.9	1.6 ± 0.9
ADI-R Childhood Communication (Mean ± SD)		0.5 ± 0.6	0.3 ± 0.5	0.9 ± 0.5	0.4 ± 0.6
ADI-R Current Communication (Mean ± SD)		0.2 ± 0.4	0.1 ± 0.4	0.5 ± 0.5	0.1 ± 0.3
ADI-R Childhood Social Interaction (Mean ± SD)		0.5 ± 0.5	0.4 ± 0.4	0.4 ± 0.3	0.9 ± 0.7
ADI-R Current Social Interaction (Mean ± SD)		0.4 ± 0.4	0.3 ± 0.3	0.3 ± 0.2	0.7 ± 0.5
ADI-R Childhood Repetitive Interests and Behaviors (Mean ± SD)		0.4 ± 0.3	0.3 ± 0.3	0.3 ± 0.2	0.5 ± 0.3
ADI-R Current Repetitive Interests and Behaviors (Mean ± SD)		0.3 ± 0.2	0.2 ± 0.3	0.3 ± 0.2	0.4 ± 0.2

*Indicates significant difference between the four diagnostic groups at $p < 0.05$

** Genotyping data not available for entire sample; percentages represent proportion of each group with available data

Table 2. *Student's t-test results for sex differences in autistic features and prodromal symptoms (n = 105)*

Variable	Sex	*n*	Mean	Std. Deviation	*t*	*p*
SIPS Positive Symptoms	Female	48	1.16	0.91	1.55	0.12
	Male	57	1.44	0.95		
SIIPS Negative Symptoms	Female	47	1.01	0.97	2.31	0.02
	Male	57	1.47	1.06		
SIPS Disorganized Symptoms	Female	48	0.78	0.91	2.23	0.03
	Male	57	1.18	0.95		
SIPS General Symptoms	Female	48	1.08	1.06	0.51	0.61
	Male	57	1.18	0.98		
ADI-R Childhood Communication	Female	48	0.39	0.52	1.26	0.21
	Male	54	0.54	0.61		
ADI-R Current Communication	Female	48	0.19	0.39	0.65	0.52
	Male	56	0.25	0.42		
ADI-R Childhood Social Interaction	Female	48	0.45	0.42	1.74	0.09
	Male	53	0.63	0.61		
ADI-R Current Social Interaction	Female	48	0.32	0.34	2.26	0.03
	Male	57	0.50	0.49		
ADI-R Childhood Repetitive Interests and Behaviors	Female	47	0.29	0.30	2.09	0.04
	Male	55	0.42	0.28		
ADI-R Current Repetitive Interests and Behaviors	Female	47	0.24	0.25	2.00	0.04
	Male	56	0.33	0.22		

Table 3. *MANCOVA univariate analyses of severity of childhood autistic features by diagnostic group (n = 97)*

Source	Dependent Variable	*df*	Mean Square	*F*	*p*	Partial eta squared
Age	*Childhood communication*	1	0.01	0.27	0.61	0.00
	Childhood social interaction	1	0.01	0.46	0.49	0.01
	Childhood repetitive interests and behaviors	1	0.00	0.01	0.92	0.00
Race	*Childhood communication*	1	0.09	2.57	0.11	0.03
	Childhood social interaction	1	0.01	0.08	0.77	0.00
	Childhood repetitive interests and behaviors	1	0.01	0.37	0.54	0.00
Diagnostic Group	*Childhood communication*	2	0.25	6.75	< 0.01	0.13
	Childhood social interaction	2	0.42	13.89	< 0.001	0.24
	Childhood repetitive interests and behaviors	2	0.08	5.92	< 0.01	0.12
Sex	*Childhood communication*	1	0.14	3.85	0.05	0.04
	Childhood social interaction	1	0.03	1.14	0.29	0.01
	Childhood repetitive interests and behaviors	1	0.04	3.00	0.09	0.03
Diagnostic group * Sex	*Childhood communication*	2	0.07	1.95	0.15	0.04
	Childhood social interaction	2	0.02	0.64	0.53	0.01
	Childhood repetitive interests and behaviors	2	0.01	0.86	0.43	0.02
Error	*Childhood communication*	89	0.04			
	Childhood social interaction	89	0.03			
	Childhood repetitive interests and behaviors	89	0.01			
Corrected Total	*Childhood communication*	96				
	Childhood social interaction	96				
	Childhood repetitive interests and behaviors	96				

Table 4. *Student's t-test analyses of severity of childhood autistic features by three diagnostic groups*

Domain		Diagnostic Group	Mean	SD	t	p
Childhood communication	Contrast	*22qDS*	0.88	0.46	5.13	< 0.001
		Control	0.29	0.48		
	Contrast	*SPD*	0.36	0.61	0.50	0.62
		Control	0.29	0.48		
	Contrast	*22qDS*	0.88	0.46	3.59	0.001
		SPD	0.36	0.61		
Childhood social interaction	Contrast	*22qDS*	0.43	0.32	0.85	0.39
		Control	0.34	0.38		
	Contrast	*SPD*	0.99	0.69	5.11	< 0.001
		Control	0.34	0.38		
	Contrast	*22qDS*	0.43	0.32	3.83	< 0.001
		SPD	0.99	0.69		
Childhood repetitive interests and behaviors	Contrast	*22qDS*	0.34	0.22	0.65	0.52
		Control	0.29	0.29		
	Contrast	*SPD*	0.50	0.32	2.89	0.005
		Control	0.29	0.29		
	Contrast	*22qDS*	0.34	0.22	2.17	0.03
		SPD	0.50	0.32		

Table 5. *MANCOVA univariate analyses of severity of current autistic features by diagnostic group (n = 102)*

Source	Dependent Variable	*df*	Mean Square	*F*	*p*	Partial eta squared
Age	*Current communication*	1	0.04	1.92	0.17	0.02
	Current social interaction	1	0.04	1.63	0.21	0.02
	Current repetitive interests and behaviors	1	0.01	0.85	0.36	0.01
Race	*Current communication*	1	0.00	0.01	0.93	0.00
	Current social interaction	1	0.01	0.43	0.51	0.02
	Current repetitive interests and behaviors	1	0.00	0.15	0.70	0.00
Diagnostic group	*Current communication*	2	0.23	10.56	< 0.001	0.18
	Current social interaction	2	0.27	12.72	< 0.001	0.21
	Current repetitive interests and behaviors	2	0.06	6.43	< 0.01	0.12
Sex	*Current communication*	1	0.05	2.15	0.15	0.02
	Current social interaction	1	0.04	1.92	0.17	0.02
	Current repetitive interests and behaviors	1	0.01	1.46	0.23	0.02
Diagnostic group * Sex	*Current communication*	2	0.03	1.43	0.25	0.03
	Current social interaction	2	0.03	1.42	0.25	0.03
	Current repetitive interests and behaviors	2	0.02	2.35	0.10	0.05
Error	*Current communication*	94	0.02			
	Current social interaction	94	0.02			
	Current repetitive interests and behaviors	94	0.01			
Corrected Total	*Current communication*	101				
	Current social interaction	101				
	Current repetitive interests and behaviors	101				

Table 6. *Student's t-test analyses of severity of current autistic features by three diagnostic groups*

Domain		Diagnostic Group	Mean	SD	t	p
ADI-R Current communication	Contrast	*22qDS*	0.52	0.46	4.19	< 0.001
		Control	0.12	0.35		
	Contrast	*SPD*	0.12	0.28	0.04	0.97
		Control	0.12	0.35		
	Contrast	*22qDS*	0.52	0.46	3.96	0.001
		SPD	0.12	0.28		
ADI-R Current social interaction	Contrast	*22qDS*	0.33	0.23	0.77	0.45
		Control	0.27	0.34		
	Contrast	*SPD*	0.72	0.55	4.41	< 0.001
		Control	0.27	0.34		
	Contrast	*22qDS*	0.33	0.23	3.58	0.001
		SPD	0.72	0.55		
ADI-R Current repetitive interests and behaviors	Contrast	*22qDS*	0.26	0.19	0.42	0.67
		Control	0.24	0.25		
	Contrast	*SPD*	0.39	0.22	2.86	0.01
		Control	0.24	0.25		
	Contrast	*22qDS*	0.26	0.19	2.49	0.02
		SPD	0.39	0.22		

Table 7. *MANCOVA univariate analyses for severity of prodromal symptoms by diagnostic group (n = 104)*

Source	Dependent Variable	df	Mean Square	*F*	*p*	Partial eta squared
Age	Positive symptoms	1	0.00	0.05	0.82	0.00
	Negative symptoms	1	0.00	0.01	0.93	0.00
	Disorganized symptoms	1	0.00	0.00	0.99	0.00
	General symptoms	1	0.00	0.05	0.83	0.00
Race	Positive symptoms	1	0.01	0.23	0.63	0.00
	Negative symptoms	1	0.00	0.08	0.78	0.00
	Disorganized symptoms	1	0.00	0.00	0.97	0.00
	General symptoms	1	0.00	0.37	0.55	0.00
Diagnostic group	Positive symptoms	2	2.94	80.03	< 0.001	0.63
	Negative symptoms	2	2.12	37.78	< 0.001	0.44
	Disorganized symptoms	2	2.10	50.63	< 0.001	0.51
	General symptoms	2	2.02	32.07	< 0.001	0.40
Sex	Positive symptoms	1	0.19	5.20	0.03	0.05
	Negative symptoms	1	0.91	16.27	< 0.001	0.15
	Disorganized symptoms	1	0.86	20.82	< 0.001	0.18
	General symptoms	1	0.19	3.09	0.08	0.03
Diagnostic group * Sex	Positive symptoms	2	0.01	0.27	0.76	0.01
	Negative symptoms	2	0.05	0.87	0.42	0.02
	Disorganized symptoms	2	0.06	1.35	0.27	0.03
	General symptoms	2	0.02	0.28	0.75	0.01
Error	Positive symptoms	96	0.04			
	Negative symptoms	96	0.06			
	Disorganized symptoms	96	0.04			
	General symptoms	96	0.06			
Corrected Total	Positive symptoms	103				
	Negative symptoms	103				
	Disorganized symptoms	103				
	General symptoms	103				

Table 8. *Student's t-test analyses of severity of prodromal symptoms by three diagnostic groups*

Domain		Diagnostic Group	Mean	SD	*t*	*p*
SIPS Positive symptoms	Contrast	*22qDS*	1.54	0.58	7.38	< 0.001
		Control	0.55	0.55		
	Contrast	*SPD*	2.30	0.61	13.01	< 0.001
		Control	0.55	0.55		
	Contrast	*22qDS*	1.54	0.58	4.88	< 0.001
		SPD	2.30	0.61		
SIPS Negative symptoms	Contrast	*22qDS*	2.04	0.84	9.13	< 0.001
		Control	0.51	0.59		
	Contrast	*SPD*	1.73	0.97	6.09	< 0.001
		Control	0.51	0.59		
	Contrast	*22qDS*	2.04	0.84	1.27	0.21
		SPD	1.73	0.97		
SIPS Disorganized symptoms	Contrast	*22qDS*	1.50	0.82	8.87	< 0.001
		Control	0.27	0.37		
	Contrast	*SPD*	1.67	0.92	7.93	< 0.001
		Control	0.27	0.37		
	Contrast	*22qDS*	1.50	0.82	0.73	0.47
		SPD	1.67	0.92		
SIPS General symptoms	Contrast	*22qDS*	1.84	0.96	8.48	< 0.001
		Control	0.42	0.49		
	Contrast	*SPD*	1.60	0.95	6.32	< 0.001
		Control	0.42	0.49		
	Contrast	*22qDS*	1.84	0.96	0.92	0.36
		SPD	1.60	0.95		

Table 9. *Correlational analyses by diagnostic group (r= Pearson correlation, z=r to z transformation)*

Variable	Sample	Childhood Communication		Current Communication		Childhood Social Interaction	
		r	*z*	*r*	*z*	*r*	*z*
Positive symptoms	22qDS	*0.32**	*0.33*	*0.08*	*0.08*	*0.11*	*0.11*
	SPD	*0.19*	*0.19*	*-0.03*	*-0.03*	*0.25*	*0.26*
Negative symptoms	22qDS	*0.09*	*0.09*	*0.11*	*0.11*	*0.09*	*0.09*
	SPD	*0.43**	*0.46*	*0.29*	*0.30*	*0.33*	*0.34*
Disorganized symptoms	22qDS	*-0.01*	*-0.01*	*-0.25*	*-0.26*	*0.09*	*0.09*
	SPD	*0.23*	*0.23*	*0.19*	*0.19*	*0.13*	*0.13*
General symptoms	22qDS	*-0.30*[a]	*-0.31*	*-0.33**	*-0.34*	*-0.07*	*-0.07*[a]
	SPD	*0.23*[a]	*0.23*	*0.09*	*0.09*	*0.42**	*0.45*[a]
Variable	Sample	Current Social Interaction		Childhood Repetitive Interests and Behaviors		Current Repetitive Interests and Behaviors	
		r	*z*	*r*	*z*	*r*	*z*
Positive symptoms	22qDS	*0.27*	*0.28*	*0.07*	*0.07*	*-0.12*	*-0.12*
	SPD	*0.25*	*0.26*	*-0.17*	*-0.17*	*-0.09*	*-0.09*
Negative symptoms	22qDS	*0.45***	*0.49*	*0.04*	*0.04*	*0.29*	*0.30*
	SPD	*0.32**	*0.33*	*0.35**	*0.37*	*0.36**	*0.38*
Disorganized Symptoms	22qDS	*0.05*	*0.05*	*0.31*	*0.32*	*0.16*	*0.16*
	SPD	*0.07*	*0.07*	*-0.06*	*-0.06*	*0.06*	*0.06*
General Symptoms	22qDS	*0.21*	*0.21*	*0.27*	*0.28*	*0.12*	*0.12*
	SPD	*0.46***	*0.49*	*0.31*	*0.32*	*0.37**	*0.39*

* Significant at $p < 0.05$, one-tailed test

** Significant at $p < 0.01$, one-tailed test

[a] Two correlations significantly differ at $p < 0.05$

Table 10. *Cluster analysis results: differences between two clusters across both 22qDS and SPD participants*

Variable	Cluster 1 (n = 28)	Cluster 2 (n = 22)
Childhood communication	1.40 ± 0.18**	1.06 ± 0.10**
Childhood social interaction	1.26 ± 0.23	1.30 ± 0.18
Childhood repetitive interests and behaviors	1.18 ± 0.11	1.21 ± 0.13
Current communication	1.24 ± 0.17**	1.00 ± 0.00**
Current social interaction	1.21 ± 0.16	1.23 ± 0.16
Current repetitive interests and behaviors	1.14 ± 0.09	1.16 ± 0.10
Positive symptoms	1.68 ± 0.17	1.66 ± 0.23
Negative symptoms	1.79 ± 0.24*	1.53 ± 0.26*
Disorganized symptoms	1.63 ± 0.26*	1.47 ± 0.23*
General symptoms	1.68 ± 0.27	1.55 ± 0.30
Age	17.75 ± 3.69	15.77 ± 4.48
Sex % Male	53.6%	40.9%
COMT Genotype % Val	50.0%	50.0%

* Clusters differ at $p < 0.05$
** Clusters differ at $p < 0.01$

Table 11. *Cluster analysis results: differences between two clusters by diagnostic group*

Variable	Diagnostic Group = 22qDS		Diagnostic Group = SPD	
	Cluster 1 (n = 21)	Cluster 2 (n = 5)	Cluster 1 (n = 7)	Cluster 2 (n = 17)
Childhood communication	1.40 ± 0.13**	1.09 ± 0.12**	1.41 ± 0.29*	1.05 ± 0.09*
Childhood social interaction	1.19 ± 0.14	1.13 ± 0.08	1.46 ± 0.35	1.35 ± 0.17
Childhood repetitive interests and behaviors	1.16 ± 0.09	1.13 ± 0.09	1.24 ± 0.14	1.23 ± 0.13
Current communication	1.25 ± 0.18**	1.00 ± 0.00**	1.21 ± 0.17*	1.00 ± 0.00*
Current social interaction	1.17 ± 0.10*	1.06 ± 0.06*	1.33 ± 0.25	1.27 ± 0.15
Current repetitive interests and behaviors	1.13 ± 0.09	1.08 ± 0.05	1.17 ± 0.09	1.19 ± 0.10
Positive symptoms	1.63 ± 0.17**	1.37 ± 0.08**	1.83 ± 0.08	1.75 ± 0.18
Negative symptoms	1.79 ± 0.23*	1.55 ± 0.14*	1.77 ± 0.29	1.52 ± 0.29
Disorganized symptoms	1.59 ± 0.27	1.48 ± 0.17	1.75 ± 0.16*	1.47 ± 0.24*
General symptoms	1.69 ± 0.29	1.65 ± 0.21	1.63 ± 0.24	1.52 ± 0.32
Sex % Male	38.1%	40.0%	100.0%	54.2%
Age	18.71 ± 3.66	21.80 ± 5.89	14.86 ± 1.95	14.00 ± 1.73
COMT Genotype % Val	50.0%	25.0%	50.0%	100.0%

* Clusters differ at $p < 0.05$
** Clusters differ at $p < 0.01$

Table 12. *Discriminant function analysis results: differences between predicted 22qDS and SPD participants*

Variable	22qDS (n = 28)	SPD (n = 25)
Childhood communication	1.35 ± 0.18**	1.14 ± 0.23**
Childhood social interaction	1.19 ± 0.15*	1.39 ± 0.23*
Childhood repetitive interests and behaviors	1.16 ± 0.10	1.22 ± 0.14
Current communication	1.21 ± 0.18*	1.05 ± 0.13*
Current social interaction	1.15 ± 0.11*	1.30 ± 0.19*
Current repetitive interests and behaviors	1.12 ± 0.08*	1.18 ± 0.09*
Positive symptoms	1.59 ± 0.18**	1.79 ± 0.16**
Negative symptoms	1.75 ± 0.23	1.59 ± 0.31
Disorganized symptoms	1.56 ± 0.26	1.58 ± 0.28
General symptoms	1.69 ± 0.25	1.56 ± 0.31
Age	18.93 ± 4.19	14.36 ± 2.12
Sex % Male	42.9%	52.0%
COMT Genotype % Val	47.8%	75.0%

* Significantly different at $p < 0.05$
** Significantly different at $p < 0.01$

Table 13. *Discriminant function analysis results: differences between predicted discriminant groups by diagnostic group*

Variable	Diagnostic Group = 22qDS		Diagnostic Group = SPD	
	22qDS (n = 26)	SPD (n = 1)	22qDS (n = 2)	SPD (n = 24)
Childhood communication	1.35 ± 0.18	1.41 ± --	1.40 ± 0.25	1.12 ± 0.22
Childhood social interaction	1.19 ± 0.13	1.27 ± --	1.33 ± 0.37	1.39 ± 0.23
Childhood repetitive interests and behaviors	1.16 ± 0.09	1.04 ± --	1.23 ± 0.18	1.23 ± 0.13
Current communication	1.20 ± 0.19	1.41 ± --	1.32 ± 0.13*	1.04 ± 0.10*
Current social interaction	1.15 ± 0.10	1.24 ± --	1.23 ± 0.21	1.31 ± 0.19
Current repetitive interests and behaviors	1.12 ± 0.09	1.07 ± --	1.09 ± 0.02	1.19 ± 0.09
Positive symptoms	1.57 ± 0.18	1.89 ± --	1.76 ± 0.12	1.78 ± 0.17
Negative symptoms	1.74 ± 0.23	1.83 ± --	1.89 ± 0.22	1.59 ± 0.32
Disorganized symptoms	1.55 ± 0.26	1.73 ± --	1.69 ± 0.16	1.57 ± 0.28
General symptoms	1.70 ± 0.25	1.73 ± --	1.61 ± 0.27	1.57 ± 0.31
% Male	38.5%	0.0%	100.0%**	41.2%**

* Clusters differ at $p < 0.05$
** Clusters differ at $p < 0.01$

Table 14. *MANCOVA univariate analyses of severity of childhood autistic features by COMT genotype (val/val, val/met, and met/met) and diagnostic group (SPD vs. control) controlling for age and race*

Source	Dependent Variable	df	Mean Square	*F*	*p*	Partial eta squared
COMT genotype	Childhood communication	2	0.02	0.48	0.63	0.04
	Childhood social interaction	2	0.06	2.26	0.13	0.15
	Childhood repetitive interests and behaviors	2	0.01	0.93	0.41	0.07
COMT genotype * Diagnostic group	Childhood communication	3	0.01	0.35	0.79	0.04
	Childhood social interaction	3	0.04	1.47	0.25	0.15
	Childhood repetitive interests and behaviors	3	0.02	1.54	0.23	0.16
COMT genotype * Sex	Childhood communication	3	0.05	1.63	0.21	0.16
	Childhood social interaction	3	0.03	1.16	0.35	0.12
	Childhood repetitive interests and behaviors	3	0.01	0.94	0.44	0.10
COMT genotype * Diagnostic group * Sex	Childhood communication	2	0.00	0.11	0.89	0.01
	Childhood social interaction	2	0.04	1.69	0.20	0.12
	Childhood repetitive interests and behaviors	2	0.01	0.61	0.55	0.05
Error	Childhood communication	25	0.03			
	Childhood social interaction	25	0.03			
	Childhood repetitive interests and behaviors	25	0.02			
Corrected Total	Childhood communication	35				
	Childhood social interaction	35				
	Childhood repetitive interests and behaviors	35				

Table 15. *MANCOVA univariate analyses of severity of current autistic features by COMT genotype (val/val, val/met, and met/met) and diagnostic group (SPD vs. control) controlling for age and race*

Source	Dependent Variable	df	Mean Square	*F*	*p*	Partial eta squared
COMT genotype	Current communication	2	0.00	0.22	0.80	0.02
	Current social interaction	2	0.02	0.93	0.41	0.06
	Current repetitive interests and behaviors	2	0.00	0.10	0.91	0.01
COMT genotype * Diagnostic group	Current communication	3	0.00	0.03	0.99	0.00
	Current social interaction	3	0.03	1.56	0.22	0.15
	Current repetitive interests and behaviors	3	0.02	2.58	0.07	0.22
COMT genotype * Sex	Current communication	3	0.02	1.13	0.36	0.11
	Current social interaction	3	0.01	0.75	0.53	0.08
	Current repetitive interests and behaviors	3	0.01	0.93	0.44	0.09
COMT genotype * Diagnostic group * Sex	Current communication	2	0.00	0.05	0.96	0.00
	Current social interaction	2	0.03	1.77	0.19	0.12
	Current repetitive interests and behaviors	2	0.01	1.36	0.27	0.09
Error	Current communication	27	0.02			
	Current social interaction	27	0.02			
	Current repetitive interests and behaviors	27	0.01			
Corrected Total	Current communication	37				
	Current social interaction	37				
	Current repetitive interests and behaviors	37				

Table 16. *MANCOVA univariate analyses for severity of prodromal symptoms by COMT genotype (val/val, val/met, and met/met) and diagnostic group (SPD vs. control) controlling for age and race*

Source	Dependent Variable	df	Mean Square	*F*	*p*	Partial eta squared
COMT genotype	Positive symptoms	2	0.01	0.11	0.90	0.01
	Negative symptoms	2	0.07	1.58	0.23	0.11
	Disorganized symptoms	2	0.07	3.31	0.05	0.19
	General symptoms	2	0.06	1.47	0.25	0.09
COMT genotype * Diagnostic group	Positive symptoms	3	0.83	16.92	< 0.001	0.65
	Negative symptoms	3	0.42	8.99	< 0.001	0.50
	Disorganized symptoms	3	0.47	23.32	< 0.001	0.72
	General symptoms	3	0.35	8.59	< 0.001	0.49
COMT genotype * Sex	Positive symptoms	3	0.01	0.23	0.88	0.03
	Negative symptoms	3	0.22	4.77	0.01	0.35
	Disorganized symptoms	3	0.06	2.96	0.05	0.25
	General symptoms	3	0.09	2.41	0.09	0.21
COMT genotype * Diagnostic group * Sex	Positive symptoms	2	0.05	1.01	0.38	0.07
	Negative symptoms	2	0.12	2.52	0.09	0.16
	Disorganized symptoms	2	0.03	1.27	0.29	0.09
	General symptoms	2	0.02	0.56	0.58	0.04
Error	Positive symptoms	27	0.05			
	Negative symptoms	27	0.05			
	Disorganized symptoms	27	0.02			
	General symptoms	27	0.04			
Corrected Total	Positive symptoms	37				
	Negative symptoms	37				
	Disorganized symptoms	37				
	General symptoms	37				

Table 17. *MANCOVA univariate analyses for severity of childhood autistic features by COMT genotype (val vs. met) and diagnostic group (SPD vs. 22qDS) controlling for age and race*

Source	Dependent Variable	df	Mean Square	*F*	*p*	Partial eta squared
COMT genotype	Childhood communication	1	0.00	0.00	0.99	0.00
	Childhood social interaction	1	0.02	1.06	0.32	0.05
	Childhood repetitive interests and behaviors	1	0.0	0.00	0.96	0.00
COMT genotype * Diagnostic group	Childhood communication	2	0.13	3.62	0.05	0.28
	Childhood social interaction	2	0.01	0.34	0.72	0.03
	Childhood repetitive interests and behaviors	2	0.00	0.38	0.69	0.04
COMT genotype * Sex	Childhood communication	2	0.04	0.95	0.40	0.09
	Childhood social interaction	2	0.01	0.45	0.65	0.05
	Childhood repetitive interests and behaviors	2	0.01	0.80	0.46	0.08
COMT genotype * Diagnostic group * Sex	Childhood communication	1	0.00	0.01	0.92	0.00
	Childhood social interaction	1	0.01	0.57	0.46	0.03
	Childhood repetitive interests and behaviors	1	0.01	1.09	0.31	0.05
Error	Childhood communication	19	0.04			
	Childhood social interaction	19	0.02			
	Childhood repetitive interests and behaviors	19	0.01			
Corrected Total	Childhood communication	25				
	Childhood social interaction	25				
	Childhood repetitive interests and behaviors	25				

Table 18. *MANCOVA univariate analyses for severity of current autistic features by COMT genotype (val vs. met) and diagnostic group (SPD vs. 22qDS)*

Source	Dependent Variable	df	Mean Square	*F*	*p*	Partial eta squared
COMT genotype	Current communication	1	0.00	0.05	0.82	0.00
	Current social interaction	1	0.01	0.63	0.44	0.03
	Current repetitive interests and behaviors	1	0.00	0.00	0.95	0.00
COMT genotype * Diagnostic group	Current communication	2	0.04	1.10	0.35	0.09
	Current social interaction	2	0.00	0.20	0.82	0.02
	Current repetitive interests and behaviors	2	0.01	1.41	0.27	0.12
COMT genotype * Sex	Current communication	2	0.09	3.07	0.07	0.24
	Current social interaction	2	0.00	0.33	0.72	0.03
	Current repetitive interests and behaviors	2	0.00	0.59	0.56	0.06
COMT genotype * Diagnostic group * Sex	Current communication	1	0.00	0.01	0.92	0.00
	Current social interaction	1	0.01	1.01	0.33	0.05
	Current repetitive interests and behaviors	1	0.01	1.65	0.21	0.08
Error	Current communication	20	0.03			
	Current social interaction	20	0.01			
	Current repetitive interests and behaviors	20	0.01			
Corrected Total	Current communication	26				
	Current social interaction	26				
	Current repetitive interests and behaviors	26				

Table 19. *MANCOVA univariate analyses of severity of prodromal symptoms by COMT genotype (val vs. met) and diagnostic group (SPD vs. 22qDS)*

Source	Dependent Variable	df	Mean Square	*F*	*p*	Partial eta squared
COMT genotype	Positive symptoms	1	0.00	0.07	0.79	0.00
	Negative symptoms	1	0.06	1.27	0.27	0.06
	Disorganized symptoms	1	0.12	1.54	0.23	0.07
	General symptoms	1	0.03	0.56	0.46	0.03
COMT genotype * Diagnostic group	Positive symptoms	2	0.11	2.98	0.07	0.22
	Negative symptoms	2	0.03	0.76	0.48	0.07
	Disorganized symptoms	2	0.25	3.28	0.06	0.24
	General symptoms	2	0.27	5.39	0.01	0.34
COMT genotype * Sex	Positive symptoms	2	0.02	0.54	0.59	0.05
	Negative symptoms	2	0.11	2.43	0.11	0.19
	Disorganized symptoms	2	0.09	1.18	0.33	0.10
	General symptoms	2	0.11	2.18	0.14	0.17
COMT genotype * Diagnostic group * Sex	Positive symptoms	1	0.04	0.95	0.34	0.04
	Negative symptoms	1	0.02	0.51	0.48	0.02
	Disorganized symptoms	1	0.01	0.11	0.75	0.01
	General symptoms	1	0.12	2.41	0.14	0.10
Error	Positive symptoms	21	0.04			
	Negative symptoms	21	0.05			
	Disorganized symptoms	21	0.08			
	General symptoms	21	0.05			
Corrected Total	Positive symptoms	27				
	Negative symptoms	27				
	Disorganized symptoms	27				
	General symptoms	27				

Table 20. *Student's t-test of differences in autistic features and prodromal symptoms between COMT Val and Met 22qDS participants (n = 27)*

Variable	Allele	*n*	Mean	SD	*t*	*p*
Positive Symptoms	met	12	1.56	0.18	0.92	0.37
	val	11	1.63	0.20		
Negative Symptoms	met	12	1.67	0.22	1.51	0.15
	val	11	1.81	0.24		
Disorganized Symptoms	met	12	1.49	0.22	1.08	0.29
	val	11	1.62	0.32		
General Symptoms	met	12	1.59	0.23	1.55	0.14
	val	11	1.77	0.31		
Childhood Communication	met	12	1.33	0.23	0.48	0.64
	val	11	1.37	0.15		
Current Communication	met	12	1.22	0.22	0.14	0.89
	val	11	1.21	0.19		
Childhood Social Interaction	met	12	1.18	0.13	0.55	0.59
	val	11	1.22	0.15		
Current Social Interaction	met	12	1.13	0.13	1.19	0.25
	val	11	1.19	0.09		
Childhood Repetitive Interests and Behaviors	met	12	1.17	0.09	0.19	0.85
	val	10	1.16	0.09		
Current Repetitive Interests and Behaviors	met	12	1.12	0.09	0.35	0.73
	val	10	1.13	0.07		

Figure 1. Severity of childhood autistic features by sex across entire sample

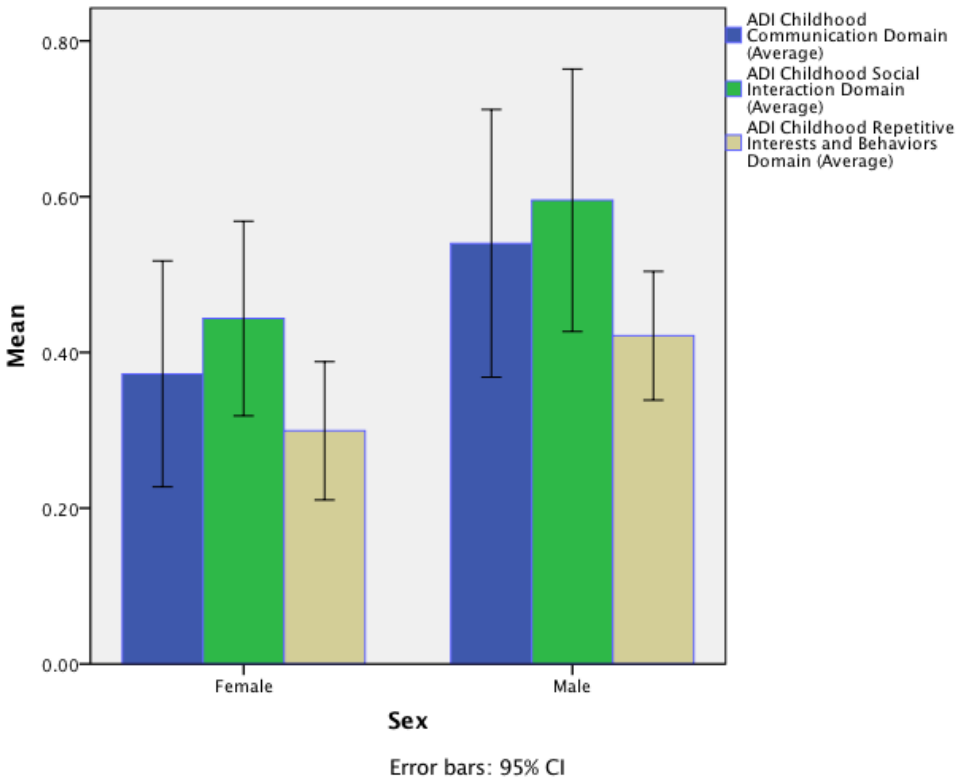


Figure 2. Severity of current autistic features by sex across entire sample

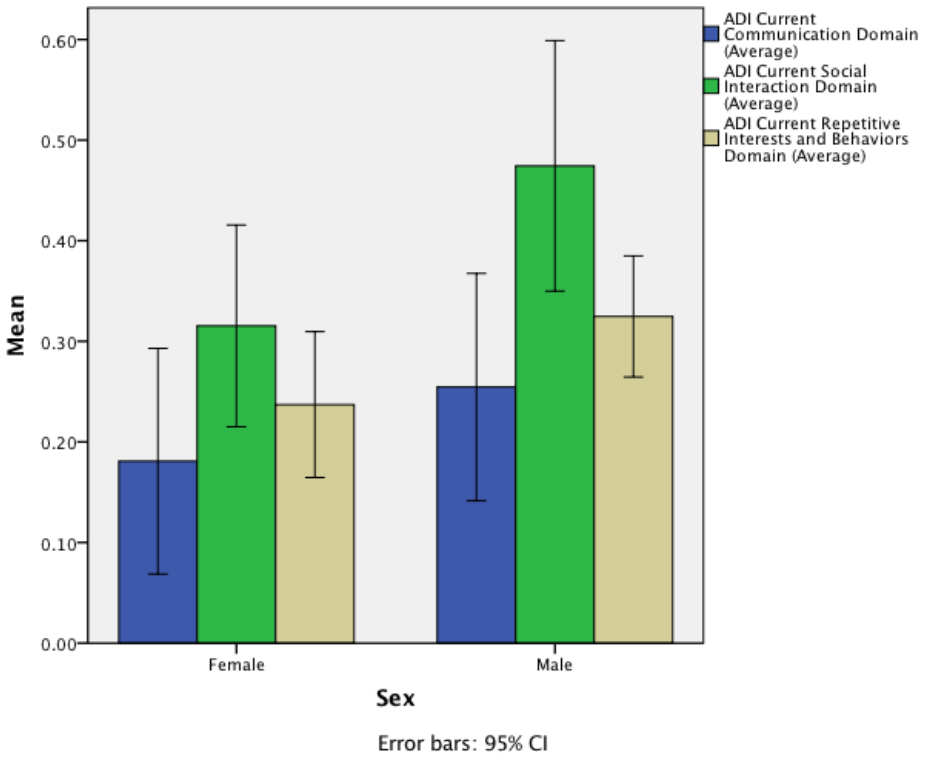


Figure 3. Severity of prodromal symptoms by sex across entire sample

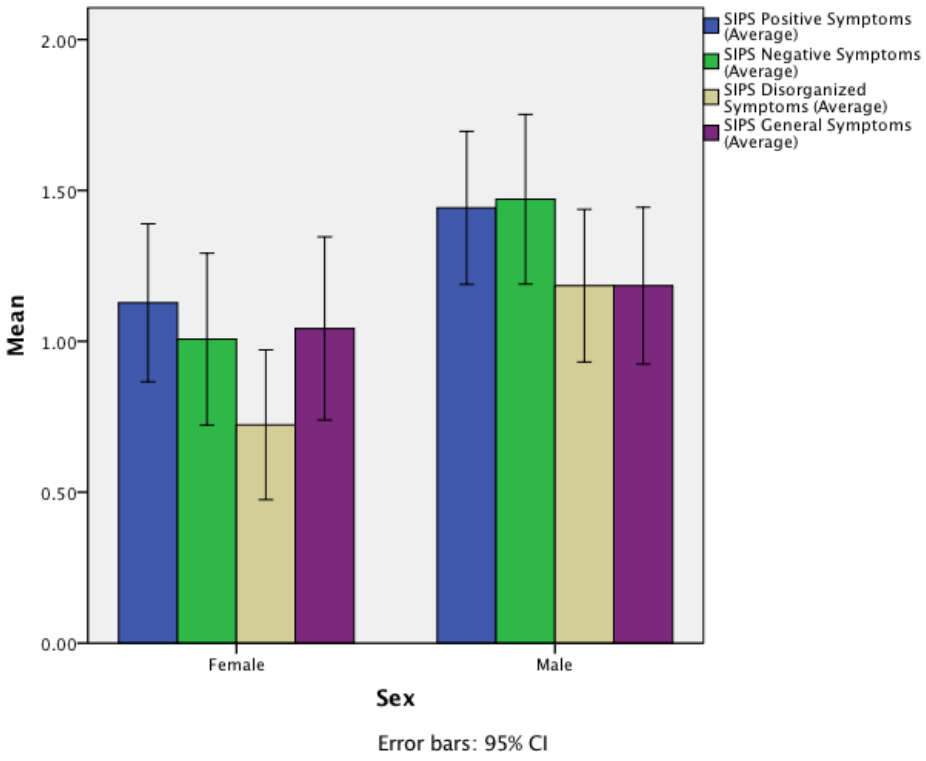


Figure 4. Severity of childhood autistic features by diagnostic group

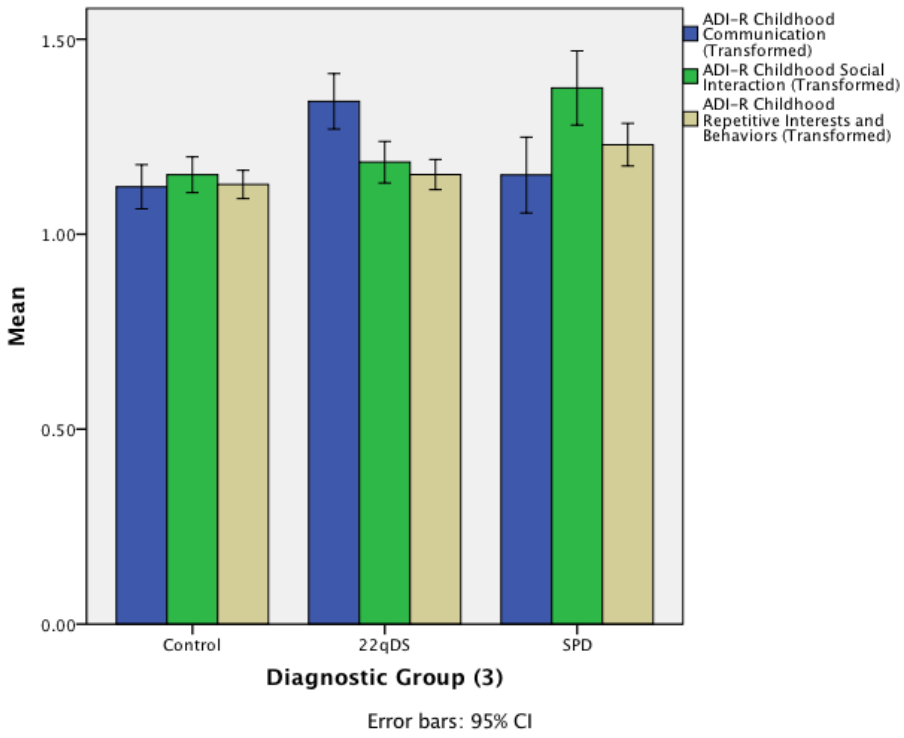


Figure 5. Severity of childhood autistic features by diagnostic group within sex

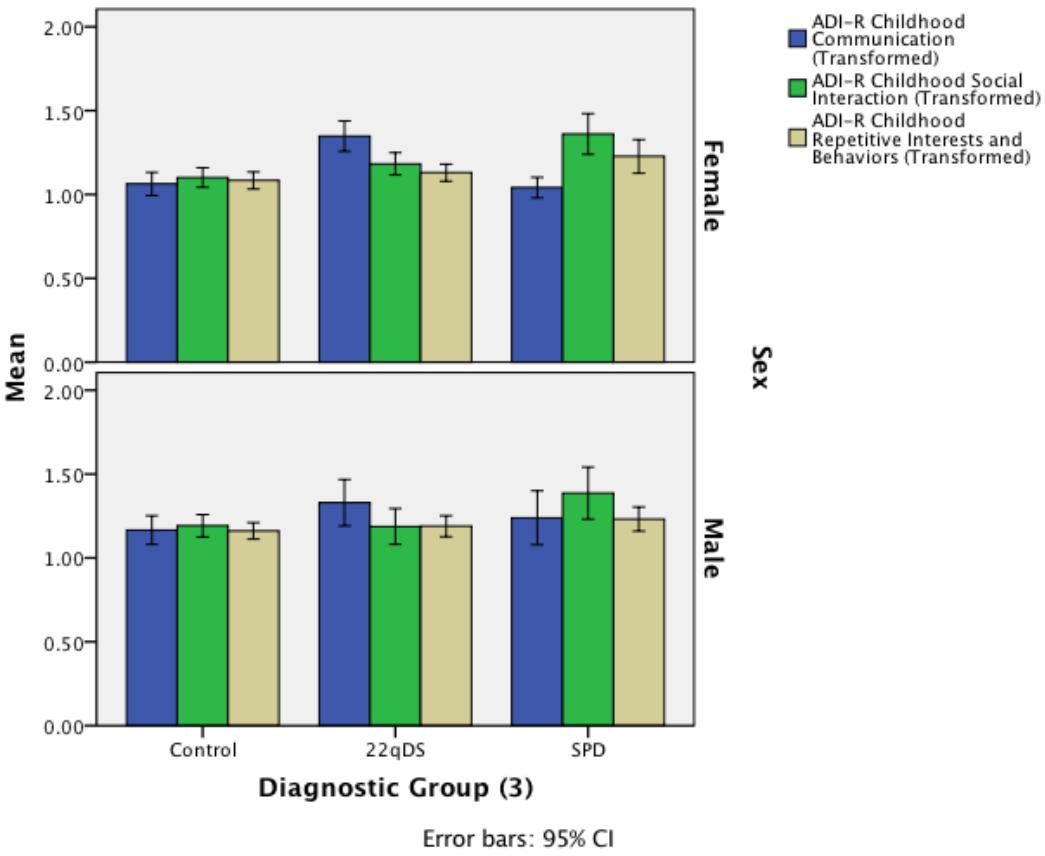


Figure 6. Severity of current autistic features by diagnostic group

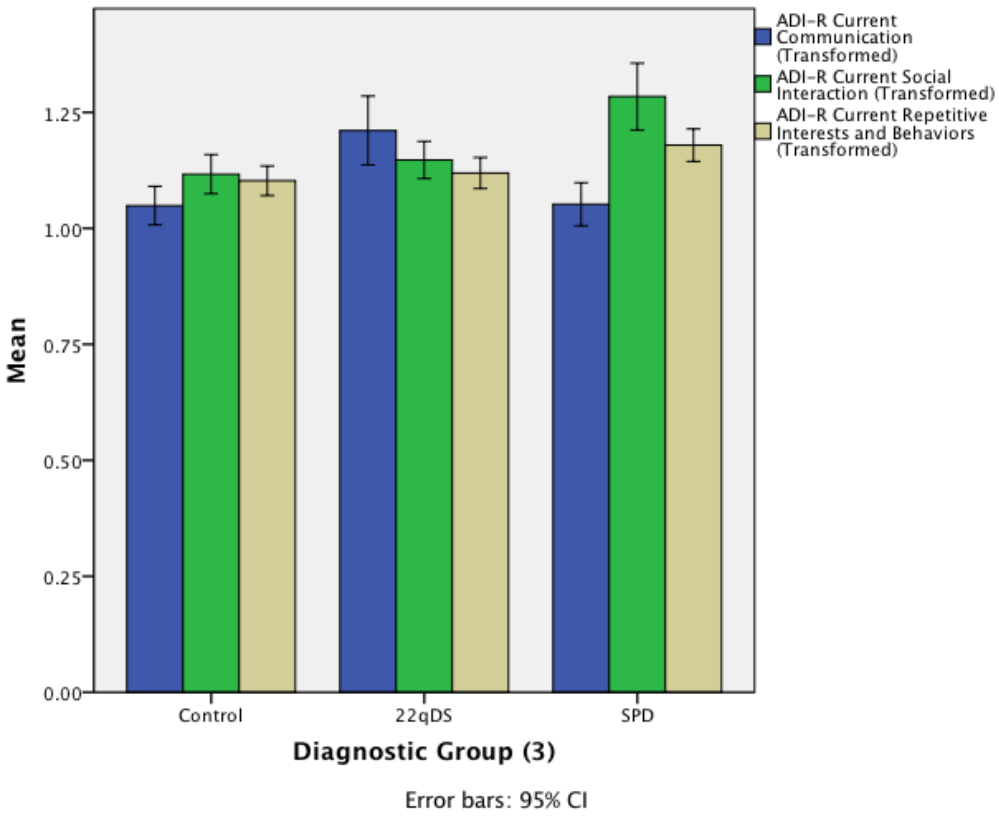


Figure 7. Severity of current autistic features by diagnostic group within sex

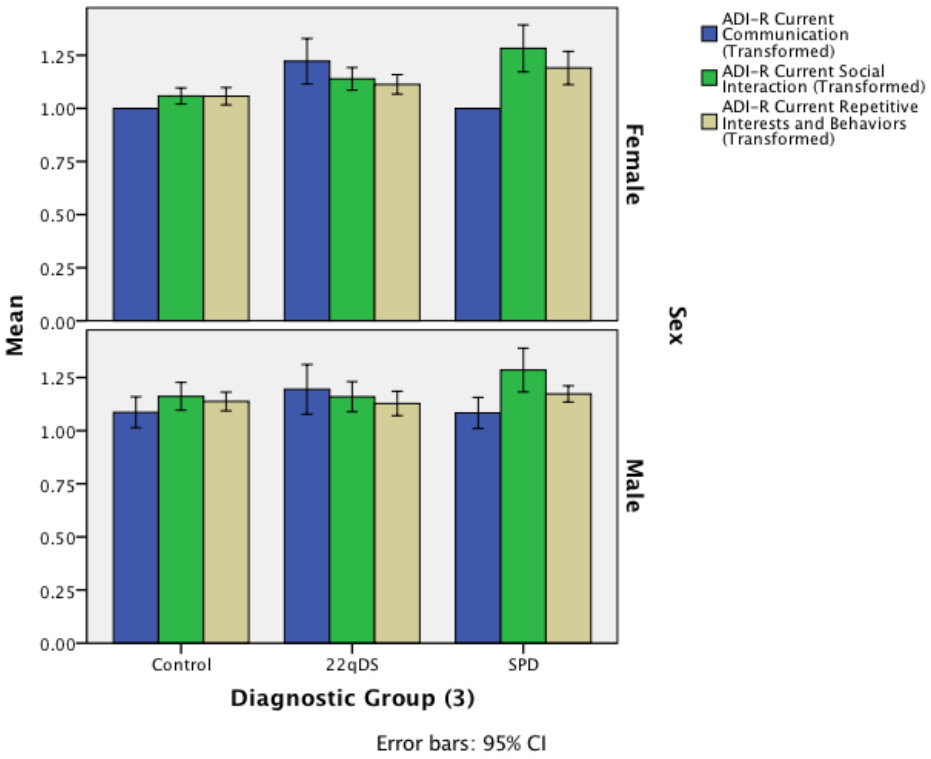


Figure 8. Severity of prodromal symptoms by diagnostic group

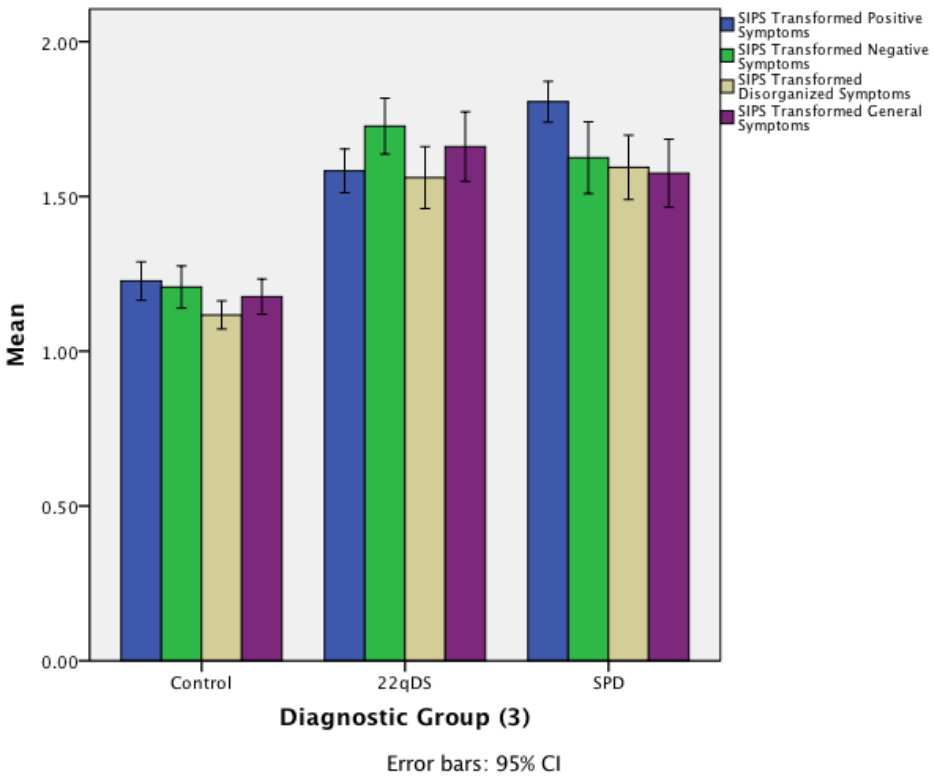


Figure 9. Severity of prodromal symptoms by diagnostic group within sex

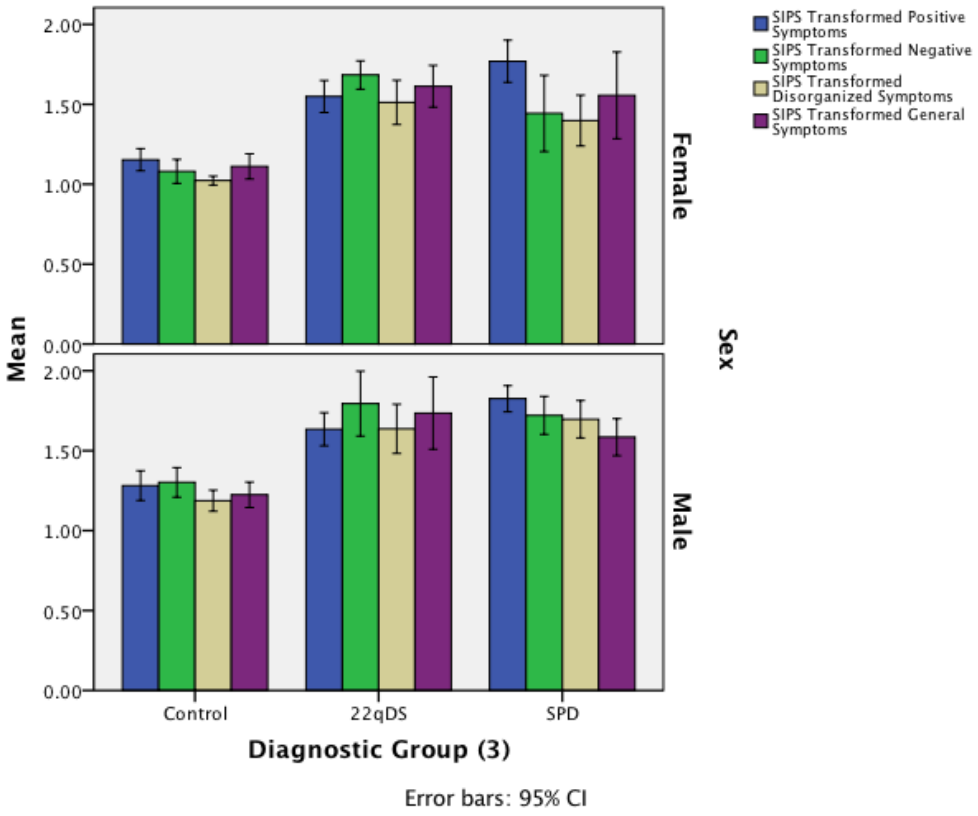


Figure 10. Differences in childhood autistic features between two clusters resulting from cluster analysis

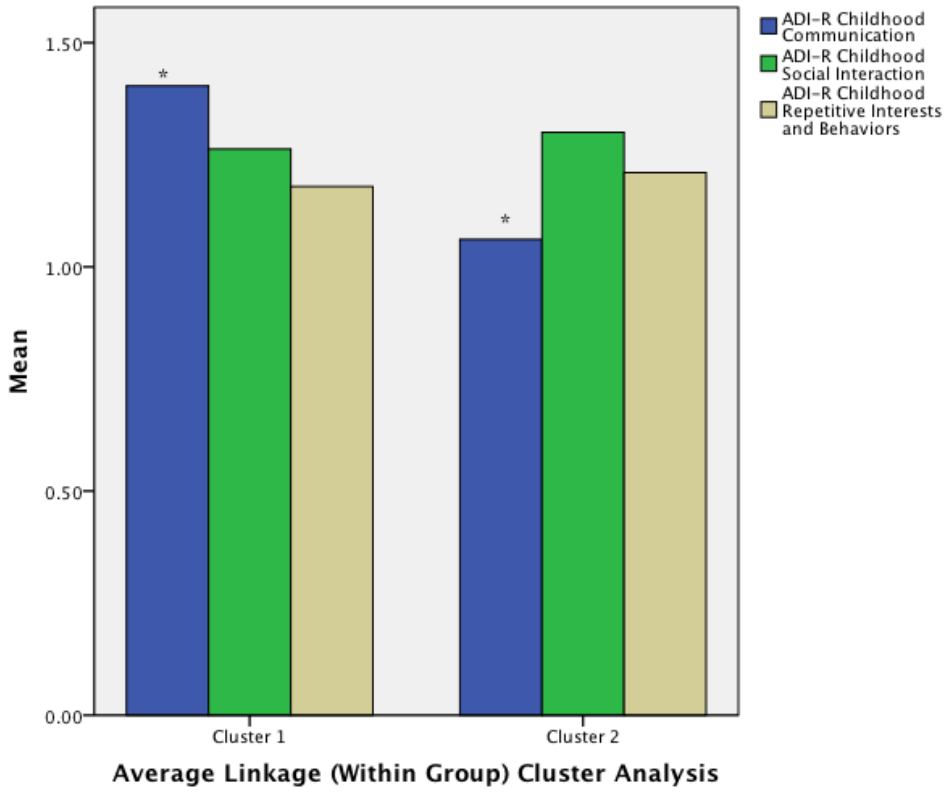


Figure 11. Differences in current autistic features between two clusters resulting from cluster analysis

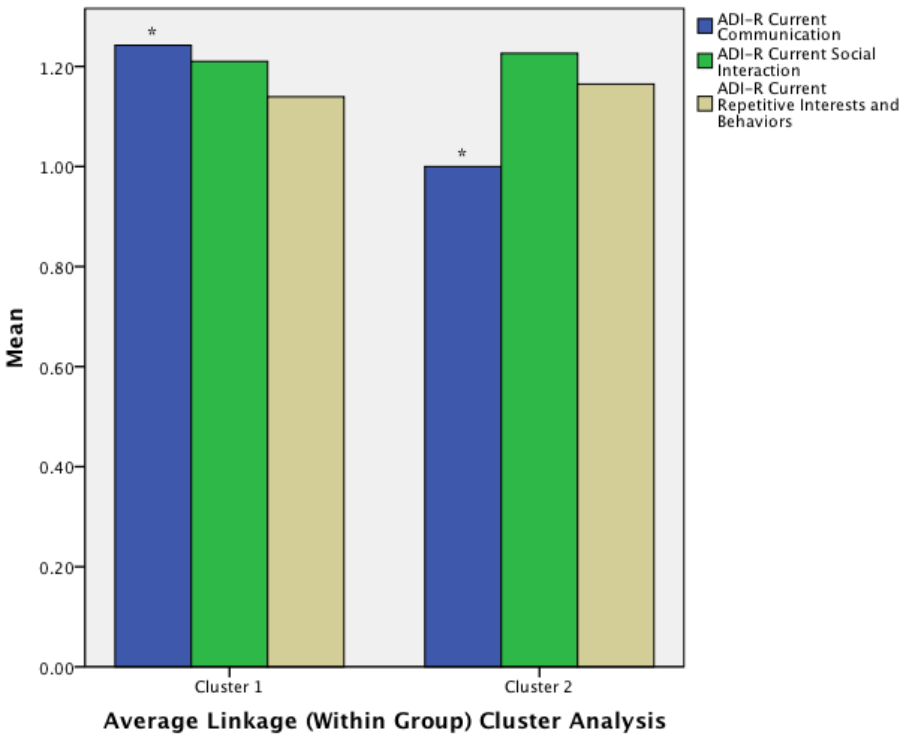


Figure 12. Differences in prodromal symptoms between two clusters resulting from cluster analysis

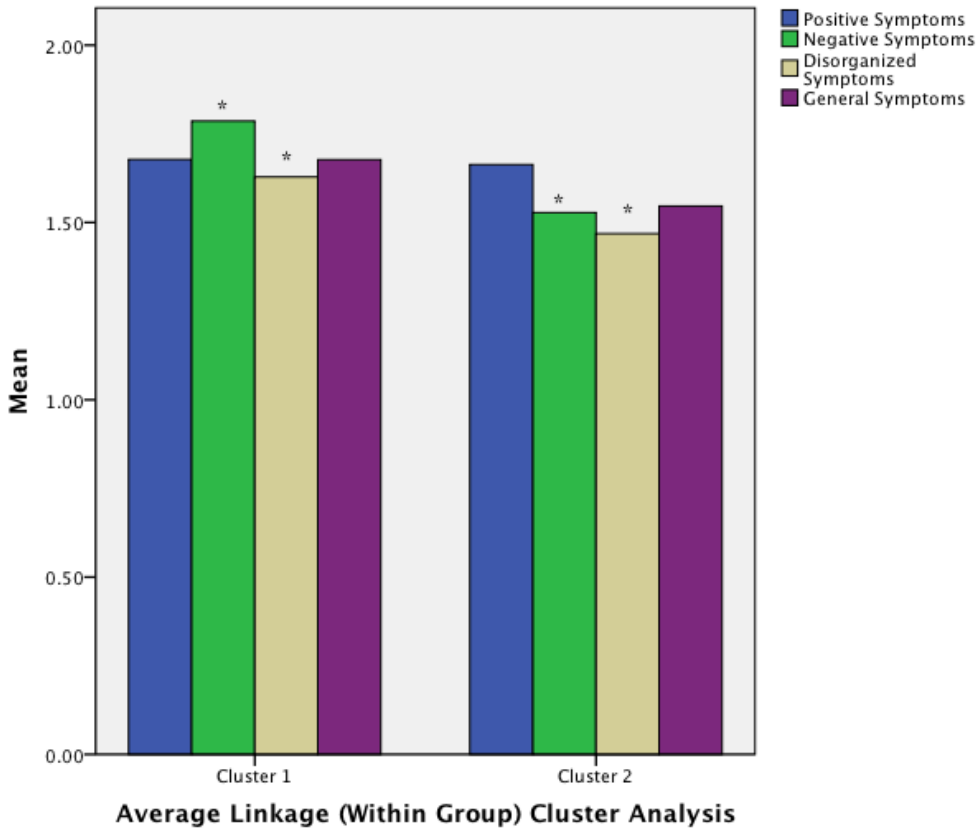


Figure 13. Differences in childhood and current autistic features between predicted SPD and 22qDS groups resulting from discriminant function analysis

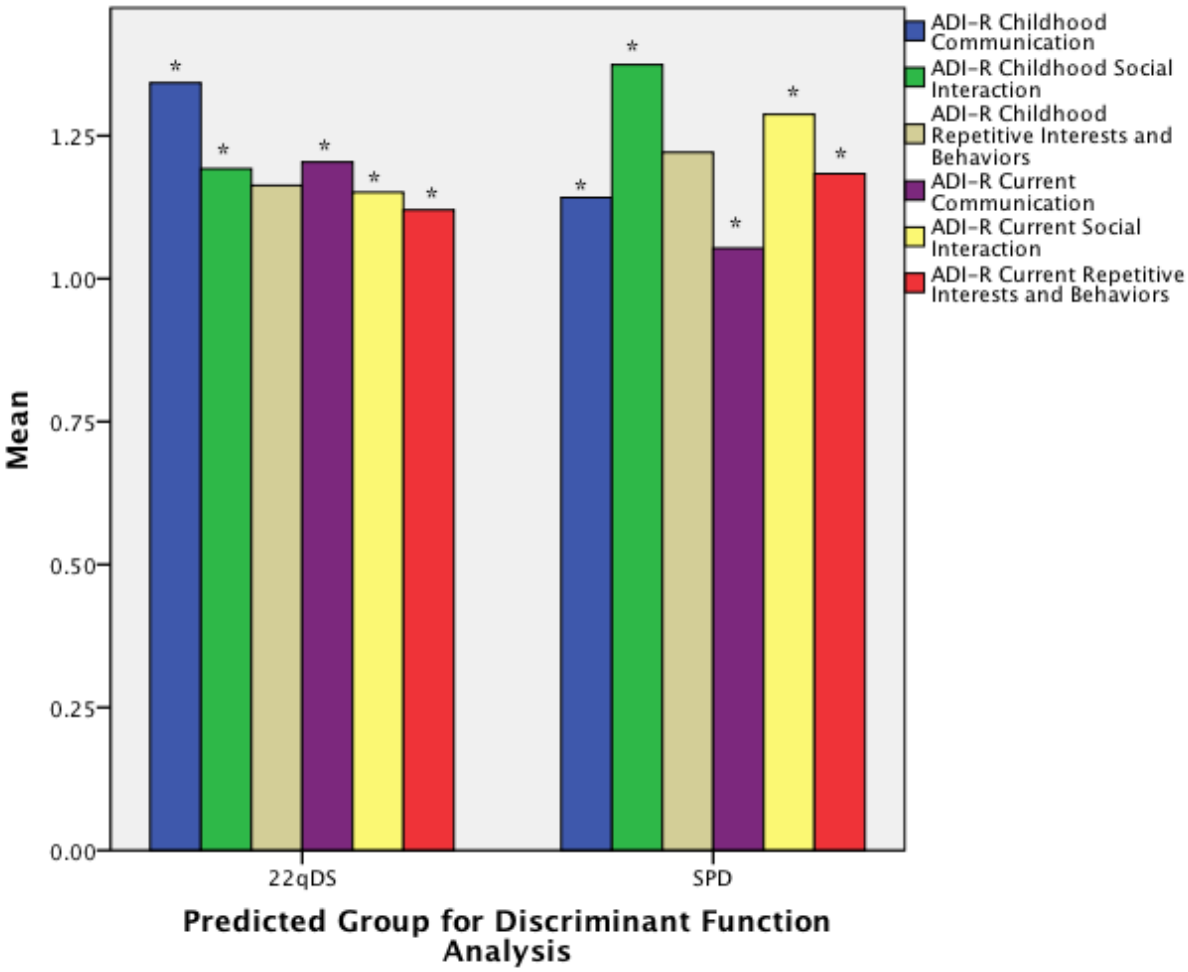


Figure 14. Differences in prodromal symptoms between predicted SPD and 22qDS groups resulting from discriminant function analysis

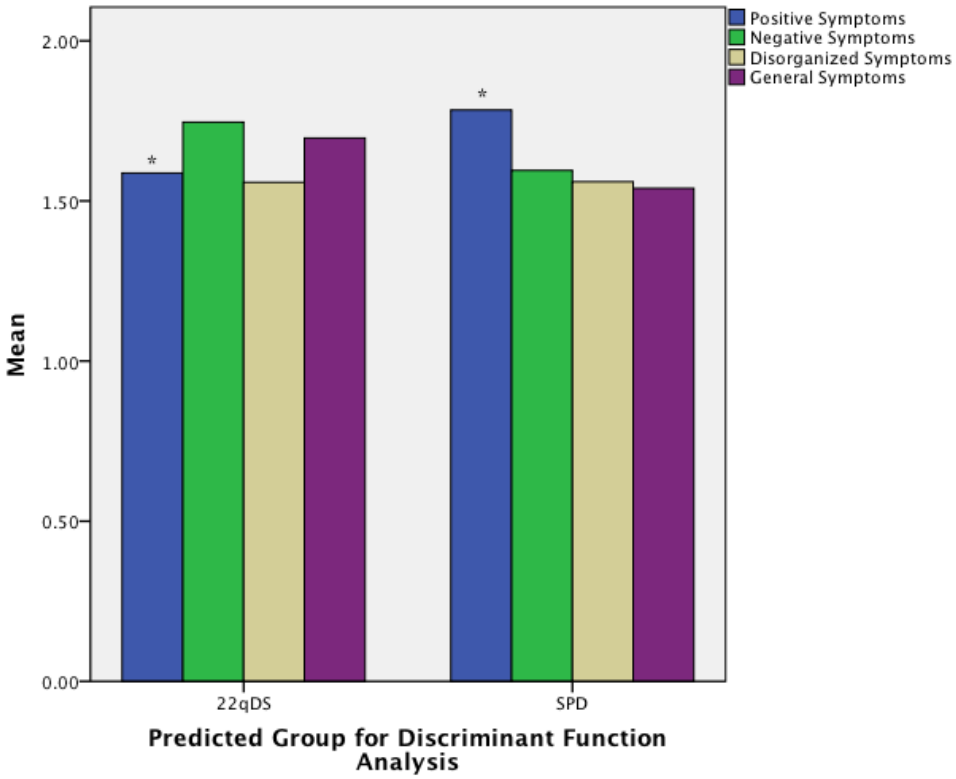


Figure 15. Interaction between COMT genotype and diagnostic group status for disorganized prodromal symptoms among control and SPD participants

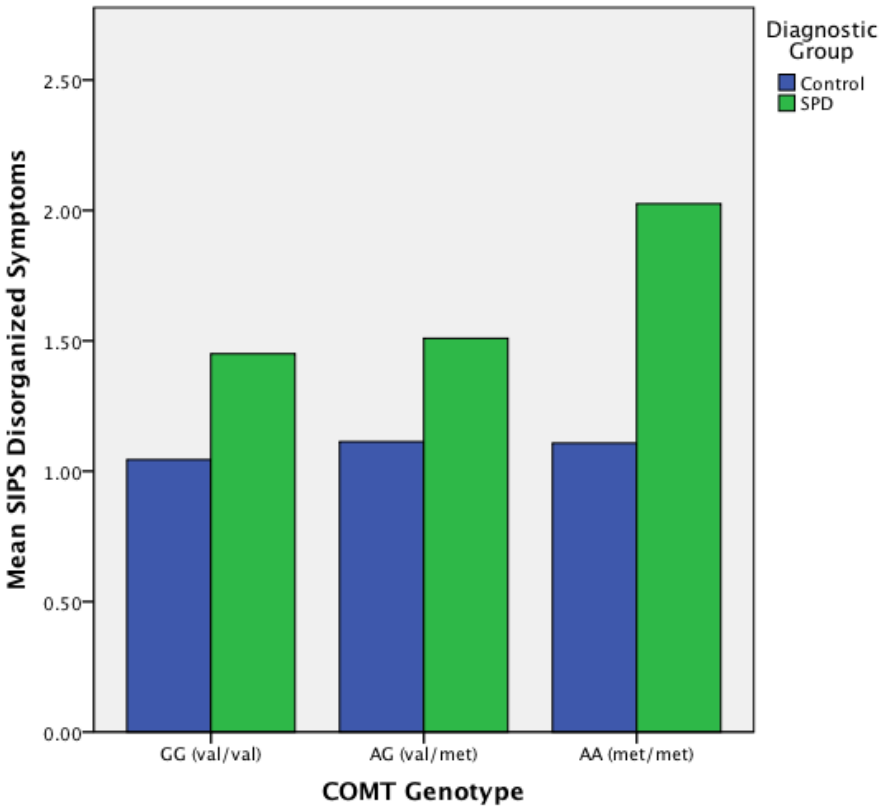
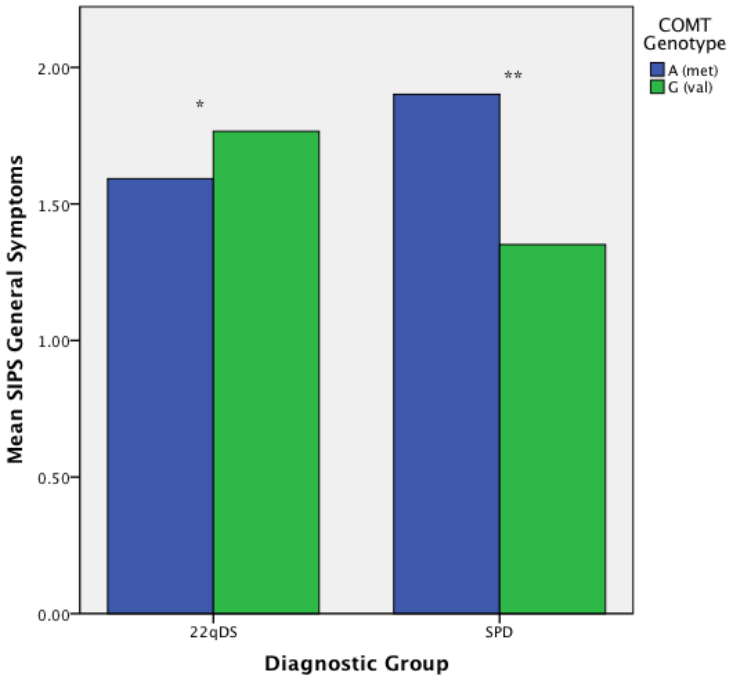
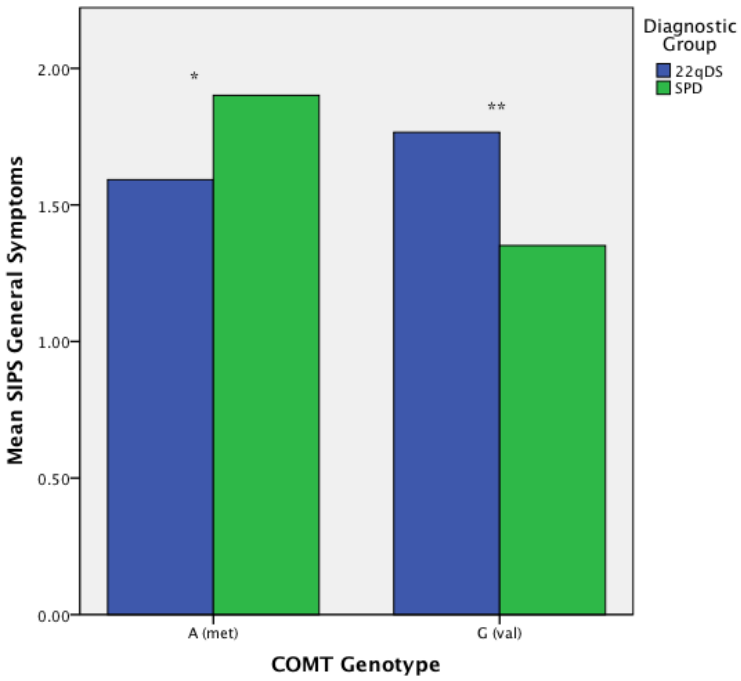


Figure 16. Interaction between COMT genotype and diagnostic group status for general prodromal symptoms among 22qDS and SPD participants



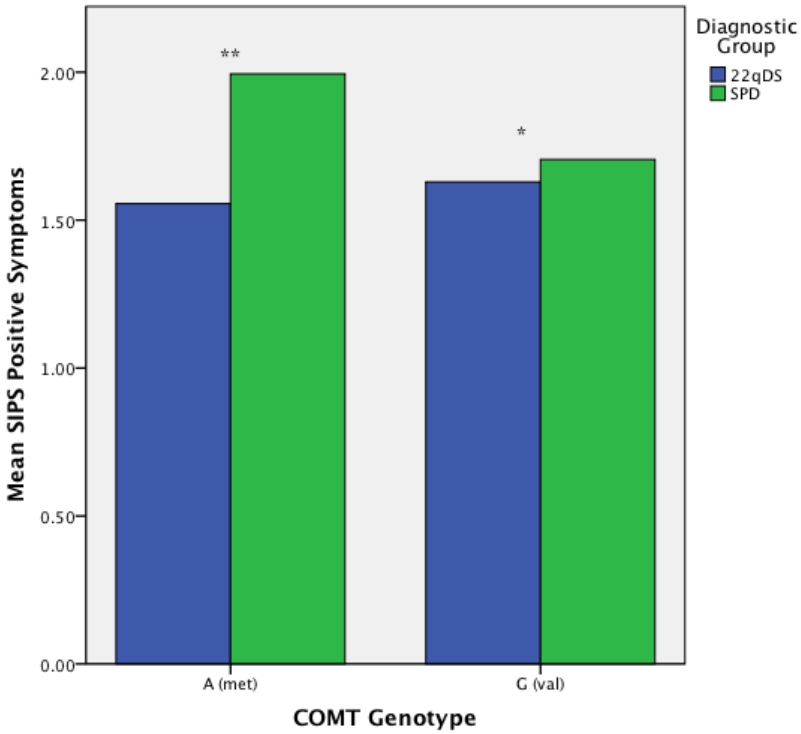
*No difference between val and met carriers
**Significant difference between val and met carriers

Figure 17. Interaction between COMT genotype and diagnostic group status for general prodromal symptoms among 22qDS and SPD participants



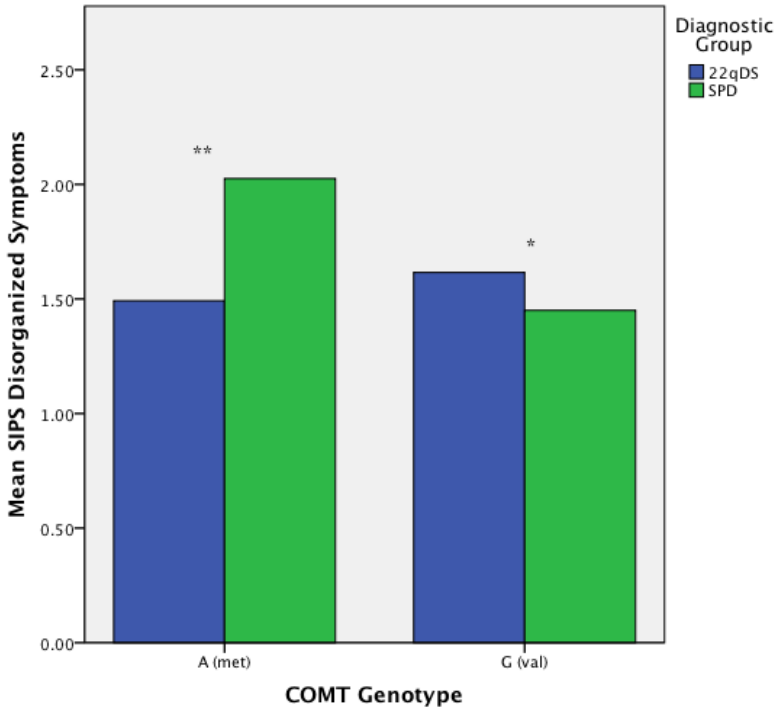
*No difference between 22qDS and SPD participants
**22qDS participants show more severe general symptoms relative to SPD participants

Figure 18. Interaction between COMT genotype and diagnostic group status for positive prodromal symptoms across 22qDS and SPD participants



*No difference between 22qDS and SPD participants
**SPD participants show more severe positive symptoms relative to 22qDS participants

Figure 19. Interaction between COMT genotype and diagnostic group status for disorganized prodromal symptoms across 22qDS and SPD participants



*No difference between 22qDS and SPD participants
**SPD participants show more severe disorganized symptoms relative to 22qDS participants