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Schizophrenia is a severe psychiatric disorder that is hypothesized to represent the most extreme manifestation of a continuum of impairment referred to as schizotypy. As such, many of the cognitive, clinical, behavioral, and neuroanatomical features of schizophrenia should be present and detectable in nonpsychotic individuals who share this vulnerability. Recent findings have led to a renewed interest in the role that the gene that codes for catechol-O-methyltransferase (COMT) plays in the development and expression of schizotypy and schizophrenia. Specifically, an amino-acid polymorphism (*Val¹⁵⁸Met*) in the COMT gene has been associated with schizophrenia based on linkage and association studies, with schizotypy in nonpsychotic adults, and with performance on dopamine-mediated prefrontal functioning in healthy adults and in patients with schizophrenia. Since abnormal functioning in dopaminergic pathways is thought to be associated with schizophrenia, COMT activity may play a role in schizophrenia pathogenesis and expression. The COMT gene is housed at 22q11.2, which maps to the commonly deleted region in 22q11 Deletion Syndrome (22q11DS), a syndrome that is associated with a highly elevated risk for the development of psychosis.

The present study investigated the relationship of COMT genotype with neuropsychological impairment and social functioning in a nonpsychotic sample of children with 22q11DS. As hypothesized, participants with the Val allele performed worse on some measures of prefrontal functioning than participants with the Met allele.

Additionally, participants with the Val allele exhibited schizophrenic-like social and behavioral deficits. Finally, associations between social and cognitive functioning and a haplotype that has been linked to schizophrenia were examined in patients with 22q11DS.

THE ROLE OF COMT IN SCHIZOPHRENIC-LIKE COGNITIVE
IMPAIRMENT AND SOCIAL FUNCTIONING IN
CHILDREN WITH 22Q11 DELETION
SYNDROME

by

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APPROVAL PAGE

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TABLE OF CONTENTS

	Page
LIST OF TABLES	v
CHAPTER	
I. INTRODUCTION	1
Schizophrenia and Schizotypy	1
Cognitive Functioning as a Marker of Schizotypy	5
Social and Behavioral Functioning as Markers of Schizotypy	6
Catechol-O-Methyltransferase and Schizophrenia	8
COMT, dopamine, and schizophrenia	9
COMT and cognitive functioning	12
Neuroimaging	15
COMT association and linkage	15
Haplotype analysis	16
Symptom and behavioral characteristics associated with COMT	18
COMT and other psychopathology	19
22q11 Deletion Syndrome	20
22q11 deletion syndrome and schizophrenia	21
Cognitive functioning in 22q11DS	22
Behavioral characteristics in 22q11DS	23
22q11DS, COMT, and schizophrenia	24
22q11DS as a genetic high-risk sample	26
Goals and Hypotheses	27
II. METHOD	32
Participants	32
Materials	33
The Continuous Performance Test	34
The Wisconsin Card Sorting Test	35
The California Verbal Learning Test – Children’s Version	36
The Wechsler Intelligence Scale for Children, 3 rd and 4 th Editions	38
The Wechsler Individual Achievement Test, 2 nd Edition	39
Computerized Diagnostic Interview Schedule for Children	39

The Child Behavior Checklist.....	39
The Social Skills Rating Scale.....	41
Genotyping.....	41
Procedure	42
III. RESULTS	43
Hypothesis 1: Neurocognitive and Intellectual Functioning	43
Hypothesis 2: Social and Behavioral Functioning.....	45
Hypothesis 3: Childhood Psychopathology	46
Hypothesis 4: Haplotype Analyses	46
IV. DISCUSSION.....	51
Cognitive Performance and COMT Genotype	52
Behavioral and Social Functioning and COMT Genotype	56
Childhood Psychopathology and COMT Genotype	59
Haplotype Analyses	61
COMT and Markers of Schizophrenia.....	63
COMT and Endophenotype Analysis	64
Neurodevelopment, Cognitive Functioning, and COMT	66
Neurodevelopment in adolescence	67
Gene-By-Gene Interactions and Haplotype Analysis	71
COMT Interactions by Sex, Environment, and Maturation.....	73
Future Directions	77
REFERENCES	79
APPENDIX A. TABLES.....	112

LIST OF TABLES

	Page
Table 1. Group Demographic Characteristics.....	112
Table 2. Means and Standard Deviations of Neurocognitive Measures by Group	113
Table 3. WISC-III Means and Standard Deviations by Group.....	114
Table 4. WIAT-II Means and Standard Deviations by Group.....	116
Table 5. CBCL Means and Standard Deviations by Group.....	117
Table 6. SSRS Means and Standard Deviations by Group.....	118
Table 7. Childhood Psychopathology and Global Functioning by Group.....	119
Table 8. Means and Standard Deviations of Neurocognitive Measures by Haplotype.....	121
Table 9. WISC-III and WIAT-II Means and Standard Deviations by Haplotype.....	122
Table 10. CBCL Means and Standard Deviations by Haplotype	124
Table 11. SSRS Means and Standard Deviations by Haplotype	125
Table 12. Cognitive Functioning in Patient with 3-Marker Haplotype	126
Table 13. Behavioral and Social Measures in Patient with 3-Marker Haplotype.....	128

CHAPTER I

INTRODUCTION

The present study examined the relationships of schizophrenic-like neurocognitive and behavioral deficits with the catechol-O-methyltransferase (COMT) *Val*¹⁵⁸*Met* polymorphism in children and adolescents with 22q11 Deletion Syndrome (22q11DS). The Val allele has been associated with a variety of features including cognitive deficits, behavior problems in children, self-reported schizotypy, and elevated rates of psychiatric disorders in 22q11DS patients, as well as in normal children and adults. Retrospective studies suggest that 22q11DS is strongly associated with the occurrence of psychotic disorders in adulthood, and is associated with specific cognitive deficits in prefrontally-mediated domains and with behavioral dysfunction. Additionally, the present work examined the relationship of proposed vulnerability haplotypes with neurocognitive and symptom measures. The present study integrates findings from the COMT, schizophrenia, 22q11DS, and schizotypy literatures to provide an integrated approach to the investigation of schizophrenic-like neurocognitive and behavioral impairment.

Schizophrenia and Schizotypy

Schizophrenia is a severe psychiatric disorder affecting approximately 1% of the general population (Gottesman, 1991; Tsuang & Faraone, 1998). Evidence from twin, adoption, and family studies indicates a substantial genetic contribution to this disorder.

However, transmission is complex, and the number of genes responsible, location of these genes, and their modes of transmission are not well understood. Schizophrenia appears to be best conceptualized as a neurodevelopmental disorder (e.g. Andreasen, 1999; Weinberger, 1987) culminating in abnormal brain organization that constitutes vulnerability to schizophrenia. A neurodevelopmental model of schizophrenia implies a neurobiological basis for pathogenesis, and such a conceptualization has led to the search for genes and neurological pathways of impact based on theoretical models and correlational evidence.

Schizotypy is defined as the personality organization that conveys risk for the development of schizophrenia, and is believed to reflect underlying neurodevelopmental disorganization (Meehl, 1962/1990; Tsuang, Stone, & Faraone, 2000). Schizotypy is expressed on a dynamic continuum of adjustment ranging from well-compensated to psychotic. This continuum of adjustment includes milder variants of the disorder such as schizotypal personality disorder, with severity contingent on the interaction of biopsychosocial factors (Gooding & Iacono, 1995). That is, vulnerability to psychosis and spectrum disorders, as well as nonclinical personality organizations that reflect mild variants of this dysmaturity, has a basis in neuromaldevelopment that may be set in motion by a number of factors. These factors may include combinations of genetic, biological, and environmental variables that disrupt neural development, organization, and functioning beginning *in utero*. These factors interact in complex ways with environmental and developmental factors resulting in both vulnerability to schizophrenia and movement along the continuum of schizotypy. For instance, Caspi et al. (2005)

found that cannabis use prior to age 15 in participants with a particular gene variant (the Val version of the *Val*¹⁵⁸*Met* polymorphism) was associated with schizophreniform disorders in early adulthood based on prospective investigation. However, cannabis use later in development evidenced no relationship to this genotype in terms of development of schizophreniform disorders. These findings highlight the complex interplay of genetic, environmental, and developmental factors in the development of psychosis.

It is assumed that the majority of schizotypes will never decompensate; however, since compensated schizotypes are hypothesized to share a common neurodevelopmental pathway with schizophrenia patients, it is expected that they will exhibit subclinical and transient clinical forms of the biological, cognitive, emotional, and behavioral features of schizophrenia. Thus, markers of vulnerability and associated features should be detectable in patients with schizophrenia-spectrum disorders and in nonpsychotic people identified as schizotypic, including first degree relatives, patients with identified genetic risk markers, and people identified by psychometric measures. Additionally, nondisordered schizotypes who exhibit these features should be more likely to develop schizophrenia-spectrum disorders.

Indeed, studies show that nonpsychotic individuals psychometrically identified as schizotypic, and people believed to share a genetic liability to schizophrenia including first degree relatives of schizophrenia patients and patients with 22q11DS, have higher rates of psychotic disorders and schizophrenia-spectrum illnesses at follow-up assessments than do control participants (Bassett & Chow, 1999; Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Erlenmeyer-Kimling et al., 2000; Kendler, Neale, &

Walsh, 1995; Kwapil, 1998; Murphy, Jones, & Owen, 1999; Pulver et al., 1994).

Longitudinal research suggests that a substantial percentage (20-40%) of youth with schizotypal symptoms go on to develop an Axis I schizophrenia spectrum disorder (Miller et al., 2002), and nonpsychotic monozygotic co-twins of schizophrenia patients appear to transmit this vulnerability to their offspring at the same rate as their schizophrenic siblings (Gottesman & Bertelsen, 1989).

Additionally, nonpsychotic schizotypes exhibit many of the cognitive, behavioral, and neurobiological features identified in schizophrenia patients, including deficits in prefrontal cognitive functioning, neurological soft signs, motor abnormalities, affective flattening, and behavioral and social skills deficits (Bearden et al., 2004; Bearden et al., 2005; Diforio, Walker, & Kestler, 2000; Erlenmeyer-Kimling et al., 2000; Gerdes et al., 1999; Lenzenweger & Dworkin, 1998; Lewandowski, Shashi, Berry, & Kwapil, 2007; Murphy et al., 1999; Swillen, Vogels, Devriendt, & Frys, 2000; Walker, Kestler, Bollini, & Hochman, 2004; Weinstein, Diforio, Schiffman, Walker, & Bonsall, 1999; Weinberger & Berman, 1988). The presence of features associated with schizophrenia in nonpsychotic individuals identified as schizotypic, together with increased risk for development of schizophrenia and spectrum disorders, supports a continuum of expression of the neurodevelopmental vulnerability to psychosis.

While genetic factors are believed to play an important role in the pathogenesis of schizophrenia, it is unlikely that a single gene or genetic variant is the sole cause of the complex constellation of cognitive, behavioral, experiential, neurochemical, and neuroanatomical traits (among others) that make up the disorder. Rather, genetic variants

may map more closely to specific features or traits associated with schizophrenia. These are likely to be features that are present and detectable prior to onset of frank psychosis and in at-risk individuals who may never decompensate.

Cognitive Functioning as a Marker of Schizotypy

It has been hypothesized that prefrontal pathophysiology is central to schizophrenia and is associated with dysregulation in dopaminergic transmission (Bertolino et al., 2000). Cognitive deficits in sustained attention, executive functioning, and working memory – functions believed to be mediated by prefrontal cortex – have been widely reported in schizophrenia patients (Aloia, Gourovitch, Weinberger, & Goldberg, 1996; Cohen, Braver, & O'Reilly, 1996; Gold & Harvey, 1993; Goldberg, Weinberger, Berman, Pliskin, & Podd, 1987; Goldman-Rakic, 1994; Green, Kern, Braff, & Mintz, 2000; Heinrichs & Zakzanis, 1998; Kuperberg & Heckers, 2002; Lenzenweger & Dworkin, 1998; Park & Holzman, 1992; Riley et al., 2000). Additionally, similar patterns of neurocognitive impairment have been reported in individuals identified as schizotypic based on diagnosis of spectrum disorders (e.g. schizotypal personality disorder), first degree relative status, and psychometric identification (Barrantes-Vidal, Caparros, & Obiols, 1999; Bergman et al., 1998; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988; Lyons et al., 1995; Minzenberg et al., 2006; Saykin et al., 1991; Voglmaier, Seidman, Salisbury, & McCarley, 1997). In children of schizophrenia patients, such deficits have been found to predict which offspring would go on to develop schizophrenia and spectrum disorders (Erlenmeyer-Kimling et al., 2000). The presence of such cognitive impairment in individuals who have been identified as schizotypic

demonstrates the existence of this cognitive profile absent the effects of medication, hospitalization, or the catastrophic nature of the disorder itself, thus lending support for cognitive dysfunction as a marker of neurodevelopmental liability.

Social and Behavioral Functioning as Markers of Schizotypy

Social impairment is a central feature of schizophrenia and, consistent with the continuum hypothesis of schizotypy, social dysfunction is detectable in patients with spectrum disorders and people identified as at-risk based on genetic liability or psychometric identification. Social impairment is widely described as a hallmark of the prodromal, active, and residual phases of schizophrenia, and it is a central feature of schizophrenia-spectrum conditions such as schizoid and schizotypal personality disorders (American Psychiatric Association, 2001). The social impairment associated with schizophrenia and spectrum disorders includes isolation, disinterest in social contact, and social anxiety. Both Kraepelin (1919) and Bleuler (1950) emphasized asociality as a feature of patients with schizophrenia, even during the premorbid phase. Social impairment, especially asociality, also played a central role in Rado's (1956) model of the development of schizophrenia, which greatly influenced Meehl's (1962, 1990) theory of schizotypy. More recently, social impairment has been described as a feature of schizotaxia, a condition that is proposed to convey the liability for schizophrenia (Tsuang et al, 2000). Likewise, social anxiety is part of the diagnostic criteria of schizotypal personality disorder, although recent formulations have limited this to paranoid expectations of mistreatment (American Psychiatric Association, 2001).

Social impairment has been found to be present in all clinical stages of schizophrenia and serves as an indicator of risk for developing the disorder in vulnerable individuals. Empirical studies indicate that impairments in social functioning prior to decompensation predict later development of schizophrenia (Cannon et al., 2001; Davidson et al., 1999; Malmberg, Lewis, David, & Allebeck, 1998). Poor social adjustment prior to first hospitalization was also associated with more days in the hospital for males who developed schizophrenia, but not for patients who developed mood disorders (Rabinowitz et al., 2005). Additionally, Johnstone, Ebmeier, Miller, Owens, and Lawrie (2005) reported that high-risk participants who developed schizophrenia during a 2½-year longitudinal assessment had more social impairment than their counterparts who remained compensated.

Family studies point to social impairment as a possible manifestation of the susceptibility for schizophrenia. Poor social adjustment has been reported in nonpsychotic people identified as schizotypic based on first-degree relative status. The Jerusalem Infant Development Study reported that adolescents with a schizophrenic parent demonstrated poorer peer engagement and more social problems than a control group (Hans, Auerbach, Asarnow, Styr, & Marcus, 2000). Additionally, the Edinburgh High-Risk Study found elevated rates of childhood social isolation in young adults identified as at-risk based on family history of schizophrenia (Hodges, Byrne, Grant, & Johnstone, 1999). Thus, social dysfunction appears to be a promising marker of risk for the development of schizophrenia, and may be indicative of underlying pathophysiology associated with vulnerability to psychosis. As such, it would be expected that social

dysfunction would be associated with genetic markers of vulnerability, even prior to decompensation.

Catechol-O-Methyltransferase and Schizophrenia

Several converging lines of evidence have led to a renewed interest in the role that the gene that codes for COMT plays in the development and expression of schizophrenia. These include the neurochemical functioning of COMT (Axelrod & Tomchick, 1958), its location, which maps to the commonly deleted region in 22q11DS (Grossman, Emanuel, & Budarf, 1992), and findings that a single nucleotide polymorphism (SNP) within the COMT gene may be associated with schizophrenic-like neurocognitive and behavioral symptoms as well as an increased risk for the development of schizophrenia and spectrum disorders (Avromopoulos et al., 2002; Bearden et al., 2005; Bearden et al., 2004; Egan et al., 2001; Glatt, Faraone, & Tsuang, 2003; Malhotra et al., 2002).

COMT is an enzyme that catalyses the O-methylation of catecholamine neurotransmitters such as dopamine, adrenaline, and noradrenalin (Axelrod & Tomchick, 1958; Karoum, Chrapusta, & Egan, 1994). That is, COMT facilitates the degradation of active dopamine and other catecholamines in the synapse, and is believed to be the major enzyme responsible for this function in prefrontal cortex (Karoum et al., 1994). A functional polymorphism with two common allelic variants (valine and methionine) affects the activity level of COMT, resulting in lower or higher levels of available catecholamines, respectively. The presence of the amino acid valine (Val) heightens activation of COMT, resulting in increased catecholamine breakdown and less available neurotransmitter. Conversely, the presence of the amino acid methionine (Met) is

associated with lower COMT activity, decreased catecholamine breakdown, and increased levels of available neurotransmitter. Functionally, homozygosity for the low-activity Met allele results in a three- to four-fold reduction of COMT activity compared with Val homozygotes (Graf et al., 2001; Lachman et al., 1996), leading to reduced degradation of synaptic catecholamines. The alleles appear to be codominant, with heterozygotes' enzyme activity midway between individuals who are Val/Val and Met/Met homozygous (Weinshilboum, Otterness, & Szumlanski, 1999).

COMT, Dopamine, and Schizophrenia. COMT activity has an important impact on prefrontal dopamine levels, as transporter mechanisms that are present in other brain regions exhibit reduced expression in prefrontal cortex, or are not expressed at all (Sesack, Hawrylak, Matus, Guido, & Levey, 1998). Dopamine has been associated with performance on tasks which recruit prefrontal cortical regions in animal models and in clinical and nonclinical human populations (Fournet, Moreaud, Roulin, Naegele, & Pellat, 2000; Medalia, Gold, & Merriam, 1988; Murphy, Arnsten, Jentsch, & Roth, 1996). Thus, COMT activity appears to affect prefrontal cognitive functioning via its effect on dopamine levels in the prefrontal cortex. Furthermore, since this region does not have active dopamine transport mechanisms, synaptic dopamine availability plays an especially important role in functions subserved by dopamine in prefrontal cortex. Indeed, COMT inhibition, which increases the availability of dopamine in the prefrontal cortex, has been associated with improved set-shifting in rats, and COMT genotype has been shown to predict cognitive performance on executive functioning and working

memory tasks – believed to be mediated by the prefrontal cortex – in humans (Egan et al., 2001; Malhotra et al., 2002; Bruder et al., 2005).

Early formulations of the role of dopamine in schizophrenia implicated hyperdopaminergic functioning in subcortical regions with the production of positive symptoms (e.g. Abi-Dargham, 2004; Carlsson, 2006 for reviews). Numerous studies supported a hyperdopaminergic model of schizophrenia; however, these findings did not address issues of negative symptoms, which in earlier formulations of schizophrenia were believed to represent the core syndrome (Bleuler, 1950; Kraepelin, 1919). More recently, reductions in dopamine functioning in prefrontal cortex have been found to be associated with negative symptoms and cognitive impairment in schizophrenia. Thus, some disconnect appears to exist between dopamine levels and symptoms in schizophrenia, with high levels in limbic regions implicated in positive symptoms and low levels in prefrontal cortex implicated in cognitive dysfunction and negative symptoms.

A “reformulated” hypothesis of the role of dopamine in schizophrenia posits that hyperdopaminergic functioning in subcortical structures is associated with positive symptoms such as hallucinations and delusions, whereas hypodopaminergic functioning in prefrontal cortical regions is associated with specific cognitive deficits seen in schizophrenia, as well as negative symptoms such as avolition and anhedonia (Abi-Dargham, 2004; Carlsson, 2006). These relationships are believed to be interdependent, as compromised cortical-subcortical structure and connectivity may play a role in dysregulation of dopamine and dopaminergic transmission. Swerdlow et al. (1995) showed that cell damage in frontal and temporal cortex increases sensitivity to effects of

dopamine receptor activation as demonstrated by disruption in sensorimotor gating of startle response in a rat model of schizophrenia. Additionally, Flagstad et al. (2004) found that late gestational disruption of neurodevelopment in rats led to behavioral changes that resemble both positive and negative schizophrenia symptoms and may be related to dysregulation of dopamine and structural brain changes including reductions in cortical and subcortical structures, dysregulation of subcortical dopamine neurotransmission, hyper-responsiveness to stress and amphetamine, and less social interaction. In a study of non-human primates, increasing levels of monoaminergic transmission in prefrontal cortex led to a gradual and significant decrease in dopamine levels in caudate nucleus (Kolachana, Saunders, & Weinberger, 1995).

In humans, Bertolino et al. (2000) demonstrated that N-acetylaspartate (NAA) levels in dorsolateral prefrontal cortex predicted subcortical dopamine function in schizophrenic patients. Furthermore, NAA measures in other cortical regions did not correlate with subcortical dopamine. Decreased NAA concentrations have been found in prefrontal regions in patients with schizophrenia (see Abbott & Bustillo, 2006 for review), and reductions of NAA in the prefrontal cortex in patients has been associated with negative symptoms based on the Positive and Negative Symptom Scales (Kay, Fiszbein, & Opler, 1987) and with poorer cognitive functioning on the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993), a task believed to tap prefrontal executive functioning. Thus, pathophysiology of the prefrontal cortex may be directly related to functional abnormalities in subcortical dopaminergic transmission,

and may be associated with many of the features commonly seen in schizophrenia, including both positive and negative symptoms.

COMT and cognitive functioning. Abnormal functioning in dopaminergic pathways is thought to be associated with schizophrenia, suggesting that COMT activity may play a role in schizophrenia pathogenesis and expression. Studies of nonhuman primates indicate that higher-level cognitive abilities depend critically on the dopaminergic projections to dorsolateral prefrontal cortex (Diamond, 1996).

Functionally, COMT has been found to predict performance on executive functioning and working memory tasks. A number of investigations have reported that the Val allele is related to poorer performance on such tasks in healthy control participants (Bilder et al., 2002; Bruder et al., 2005; Malhotra et al., 2002). Egan et al. (2001) reported that the Val allele is associated with poorer performance on the WCST, a test of executive processing believed to tap prefrontal cortical functioning (Chelune & Baer, 1986). Additionally, Bruder et al. (2005) found that COMT genotypes were associated with performance differences on specific aspects of working memory tasks, but not others. They reported that people with the Val/Val genotype performed worse than people with the Met/Met genotype on higher-order cognitive functions such as mental manipulation as measured by the WCST and the Letter-Number Sequencing Task, but that COMT genotype was not associated with more basic storage and maintenance functions as measured by the Spatial Delayed Response Task (Stratta et al., 1999), Word Serial Position Test (Wexler, Stevens, Bowers, Sernyak, & Goldman-Rakic, 1998), and N-back (1- and 2-back) (Braver et al., 1997).

The relationship between *Val*¹⁵⁸*Met* genotype and prefrontal functioning has been shown in patients with schizophrenia, as well. In patients with schizophrenia, the *Val* allele has been associated with poorer performance on prefrontally-mediated neurocognitive tasks including executive functioning, processing speed, and attention compared with patients with *Met/Met* genotypes (Bilder et al., 2002; Goldberg et al., 2003; Han et al., 2006; Weinberger et al., 2001; Woodward, Jayathilake & Meltzer, 2007). Additionally, schizophrenia patients with at least one *Val* allele exhibited P-300 amplitudes and electrophysiological markers of prefrontal dysfunction, as well as poor performance on the Stroop (Ehlis, Reif, Herrman, Lesch, & Fallgatter, 2007), and neuromotor deficits (Galderisi et al., 2005). The *Val* allele has been associated with cognitive deterioration in schizophrenia patients in a linear fashion, such that more *Val* alleles were associated with greater cognitive decline (Mata et al., 2006). Similar findings have been reported in patients with schizotypal personality disorder, with the *Val* allele associated with poorer performance on the WCST and the Paced Auditory Serial Addition Test (Gronwall, 1977), a test of sustained attention (Minzenberg et al., 2006).

The *Val* allele has also been associated with poor prefrontal cognitive functioning in people identified as at-risk for the development of schizophrenia. Goldberg et al. (2003) found the same deficits in *Val/Val* unaffected siblings of schizophrenia patients as in the patients themselves, with *Val* homozygous siblings performing worse than *Met* homozygous siblings on a test of executive functioning. Additionally, COMT was associated with performance on the WCST in patients with schizophrenia and their

unaffected siblings in a dose-dependent fashion, such that increasing Val load was associated with increasing deficits in perseverative errors (Egan et al., 2001).

Recent evidence suggests that the effect of antipsychotic medication on prefrontal functioning is moderated by genotype. Not only were executive functions and working memory better in schizophrenia patients with the Met allele, but treatment with antipsychotic medications improved cognitive performance in these domains in patients with the Met allele significantly more than in patients with the Val allele (Weickert et al., 2004; Woodward et al., 2007). These findings suggest that the *Val¹⁵⁸Met* polymorphism is associated with differential prefrontal cognitive performance, and changes in cognitive functioning associated with pharmacological treatment may be mediated by COMT genotype.

It should be noted that not all reports confirm the association between the Val allele and cognitive deficits in patients with schizophrenia or in patients identified as schizotypic. For instance, in a sample of Chinese patients with schizophrenia, the COMT *Val¹⁵⁸Met* polymorphism was not significantly associated with global cognitive function, or with symptoms or prognosis (Tsai, Hong, Liao, Lai, & Liou, 2004), and Stefanis et al. (2004) failed to detect differences in cognitive functioning by genotype in nonpsychotic males psychometrically identified as schizotypic. However, the relationship of COMT with schizophrenia, the role of COMT in cognitive functioning via dopaminergic activity, and a rich literature of specific cognitive deficits in prefrontally-mediated tasks in schizophrenic patients and people identified as vulnerable provides a possible

mechanistic rationale for the examination of the role of COMT in the pathogenesis of schizophrenia.

Neuroimaging. Given the relationships among COMT, dopaminergic functioning, neurocognitive performance, and schizophrenia, neuroimaging studies would be expected to demonstrate functional and/or structural differences between people based on genotype. The COMT Val allele has been associated with reduced gray matter density in anterior cingulate cortex and right middle temporal gyrus compared to people with the Met genotype (McIntosh et al., 2007; Ohnishi et al., 2006). Schizophrenic patients homozygous for the Val allele also showed a significant reduction of volumes in the bilateral Anterior Cingulate Cortex, as well as left amygdala-uncus, right middle temporal gyrus and left thalamus compared to patients with the Met allele (Ohnishi et al., 2006). Functionally, Met allele load had been shown to predict a more efficient physiological response in prefrontal cortex, while the Val allele has been associated with greater engagement of the prefrontal cortex when controlling for output (Bertolino et al., 2006; Egan et al., 2001). This indicates that the Val allele is associated with less efficient neurological processing on tasks of prefrontal functioning than the Met allele, even when task performance does not differ, suggesting that brain functioning in prefrontal cortex is compromised.

COMT association and linkage. Association studies have identified a number of schizophrenia susceptibility loci, among including genes in the chromosome 22q11 region such as COMT (Berrettini, 2000; McGuffin, Tanden & Corsico, 2003; Owen, Williams, & O'Donovan, 2004). Wonodi, Stine, Mitchell, Buchanan, & Thaker (2003)

found a significant association between Val allele frequency in schizophrenic patients compared to control participants, consistent with findings by Kremer et al. (2003). Family linkage studies have reported preferential transmission of the Val allele from parents to offspring with psychosis, and this result reached statistical significance when combined with another family linkage study (Glatt, Faraone, & Tsuang, 2003; Kunugi et al., 1997). McIntosh et al. (2007) found that the Val allele increased risk for schizophrenia in biological relatives in a dose-dependent fashion, such that increasing Val allele load was associated with increasing risk for the development of the disorder. Additionally, the COMT Val allele was associated with schizophrenia in a large sample of Ashkenazi Jews, and the association was even stronger when a COMT haplotype, which included the Val allele, was examined (Shifman et al., 2002). These findings support an association between COMT and schizophrenia; however, the nature of the association is unclear. COMT may confer risk directly, may exhibit combined effects on outcome with additional polymorphisms within the COMT gene, or may be in linkage disequilibrium with a different susceptibility gene (Li et al., 1996; Shifman et al., 2002). It should be noted, however, that several studies found no association between COMT *Val*¹⁵⁸*Met* genotype and schizophrenia (Bassett et al., 2007; Fan et al., 2005; Williams et al., 2005).

Haplotype analysis. Within the COMT gene, *Val*¹⁵⁸*Met* is just one of a number of polymorphic alleles. Several other candidate alleles have been examined including rs165599, rs737865, and the P2 promoter region [-278A/G; rs2097603], one or more of which has been associated with risk for schizophrenia in multiple reports (Chen, Wang,

O'Neill, Walsh, & Kendler, 2004; Li et al., 2000; Sanders et al., 2005; Shifman et al., 2002). Additionally, haplotype analyses have produced promising results by examining the association of multiple markers in the COMT gene with psychopathology. Shifman et al. (2002) found that a three-marker COMT haplotype was significantly associated with schizophrenia in a large sample of Ashkenazi Jews. This haplotype included *Val*¹⁵⁸*Met*, as well as markers rs737865 and rs165599, with the G allele associated with risk in all three markers (this included the Val allele for COMT). While the Val allele itself was significantly associated with schizophrenia, results indicated that the haplotype improved prediction significantly over any of the alleles alone. A large case-control study examined the relationship of the above haplotype, including rs737865, *Val*¹⁵⁸*Met*, and rs165599, in patients with psychosis (both mood and non-mood) and mood disorders (Funke et al., 2005). Cases were patients with schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, psychotic disorder NOS, or depressive disorder NOS. The findings indicated that *Val*¹⁵⁸*Met* and rs165599 were associated with a broad “all affected” group, and that the “opposite” (A-A-A) haplotype (and G in the P2 promotor regions [-278A/G; rs2097603]) was significantly underrepresented in the “all affected” group, suggesting that this haplotype may offer some protective benefit.

Haplotype research appears promising; however, the *Val*¹⁵⁸*Met* polymorphism continues to be of interest in and of itself, as the functional implications of variation at this locus in terms of neurochemistry are well-described. Such an understanding of the functional results of variation at other COMT loci associated with schizophrenia has not yet been achieved.

Symptom and behavioral characteristics associated with COMT. The relationship of COMT with other symptoms of psychosis has been less well studied in patients with schizophrenia; however, a recent report indicated that first-episode schizophrenia patients homozygous for the Val allele exhibited more inappropriate affect than patients with the Met/Met or Val/Met genotypes, while Met/Met and Val/Met patients had higher aggression scores (Han et al., 2006). In contrast, Tsai et al. (2004) did not find differences in symptomatology based on genotype in patients with chronic schizophrenia, although their measures were more general assessments of mental status and social and occupational functioning. Furthermore, the consequences of chronic schizophrenia may offset such differences. These findings suggest that COMT may be associated with specific aspects of functioning and symptomatology rather than general level of functioning.

Recent investigations have found higher rates of self-reported schizotypy in nonpsychotic males who were Val/Val homozygous than in Val/Met heterozygotes or Met/Met homozygotes, especially on negative and disorganized dimensions (Avramopoulos et al., 2002; Stefanis et al. 2004). Similar findings were reported in a sample of control participants and unaffected siblings of schizophrenic and bipolar patients, with the Val allele associated with self-reported schizotypy (Schurhoff et al., 2007). Such behavioral difficulties have been associated with poor premorbid adjustment in people who develop schizophrenia based on retrospective reports and prospective follow-up (Bearden et al., 2000; Cannon et al., 1997; Jones, Rodgers, Murray, & Marmot, 1994). Thus, recent findings suggest that the COMT *Val*¹⁵⁸*Met* polymorphism plays a

role in complex, dopamine-mediated prefrontal functioning, and that the Val allele is associated with schizophrenia-like neurocognitive deficits. Additionally, COMT genotype may play a role in behavioral and symptom indicators of vulnerability to schizophrenia.

COMT and other psychopathology. COMT has been associated with other psychopathology, as well, although findings tend to be mixed. Driven by the functional implications of the *Val*¹⁵⁸*Met* polymorphism's effects on prefrontal catecholamine activity, disorders that have been hypothesized to involve dysregulation of these processes have been investigated, including Attention Deficit/Hyperactivity Disorder (AD/HD) and conduct disorder, which involve deficits in executive functioning and behavioral inhibition. While some reports indicate that AD/HD, conduct disorder, and antisocial behavior are associated with the Val allele (Thapar et al., 2005), many others have failed to find an association between genotype and these disorders (Cheuk & Wong, 2006).

Smolka et al. (2005) noted that the distribution of the Val allele in the general population, which is near 50% (Palmatier, Kang, & Kidd, 1999), is surprising given its seemingly deleterious effect on prefrontal functioning. It has been suggested that the Met allele may be associated with risk factors as well, perhaps for anxiety and mood pathology (Enoch, Xu, Ferro, Harris, & Goldman, 2003). Indeed, the Met allele has been associated with panic disorder (Woo et al., 2004), major depression (Ohara, Nagai, Suzuki, & Ohara, 1998b), obsessive-compulsive disorder (Karayiorgou et al., 1999), and bipolar disorder (Papolos, Veit, Faedda, Saito, & Lachman, 1998), and with ratings of

anxiety and negative affect (Enoch et al., 2003). Gothelf et al. (2006) found an association with Met and AD/HD and OCD in patients with 22q11DS. Additionally, Smolka et al. (2005) found that the number of Met alleles was associated with limbic and prefrontal brain response to negative but not positive visual stimuli. It should be noted that they did not find any differences in depression or anxiety based on genotype, suggesting that genotype may be associated with patterns of neural activation in response to negative affective stimuli, but not with affective traits in normal subjects. Again, however, a number of other reports have failed to find associations between genotype and mood disorders, obsessive-compulsive disorder, and anxiety and phobic disorders (Azzam & Mathews, 2003; Cusin et al., 2002; Lachman, Kelsoe, Moreno, Katz, & Papolos, 1997; Ohara, Nagai, Suzuki & Ohara, 1998a; Samochowiec et al., 2004), and Domschke et al. (2004) actually found an association between panic disorder and the Val allele in women.

22q11 Deletion Syndrome

As noted above, the COMT gene maps to the commonly deleted region in 22q11DS, meaning that this genetic syndrome provides a unique vehicle for studying the effects of COMT and vulnerability for schizophrenia. 22q11DS is the most common microdeletion syndrome known in humans, affecting approximately 1 in every 2,000 to 4,000 live births (Shprintzen, 2000). 22q11DS subsumes several conditions including DiGeorge Syndrome and Velo-Cardio-Facial Syndrome (VCFS), and is the result of a hemizygous deletion at band 11.2 on the long arm of chromosome 22 (Shprintzen, 2000). The syndrome has been widely linked to a variety of medical, cognitive, and

psychosocial deficits (Bassett & Chow, 1999; Bearden et al., 2004; Bearden et al., 2005; Gerdes et al., 1999; Murphy et al., 1999; Swillen et al., 2000). Major congenital deficits include cardiac abnormalities, velopharyngeal insufficiency with or without a cleft palate, characteristic facial dysmorphology, hypoparathyroidism, and suppressed immune functioning (Shprintzen, 2000). While the deleted area can be variable and can involve deletions as large as 3Mb, the COMT gene is located in the 1.5 Mb “commonly-deleted” region in 22q11DS, meaning that all patients with 22q11DS have COMT haploinsufficiency.

22q11 deletion syndrome and schizophrenia. Retrospective findings have linked 22q11DS with a markedly elevated rate of psychotic disorders such as schizophrenia and bipolar disorder (e.g., Bassett & Chow, 1999; Bassett et al., 1998; Gothelf et al., 1997; Papalos et al., 1996; Yan et al., 1998). Murphy et al. (1999) reported that 24% of their sample of adult patients with VCFS was diagnosed with schizophrenia, and Pulver et al. (1994) reported that 31% of their sample of individuals with 22q11DS met criteria for schizophrenia or schizoaffective disorder. These studies suggest that the risk for schizophrenia and spectrum disorders among populations with 22q11DS is 25 to 30 times that of the general population. By comparison, research has not provided comparable evidence of an elevated risk for schizophrenia among individuals with other clearly identified genetic syndromes (Bassett & Chow, 1999). Studies investigating the presence of 22q11 deletions in schizophrenic populations have yielded rates between 1% and 6%, representing a 40-240 fold increase over the rate of 22q11.2 deletions in the general population (Horowitz, Shifman, Rivlin, Pisante, & Darvasi, 2005; Karayiorgou et al.,

1995; Usiskin et al, 1999; Yan et al., 1998). These findings represent the strongest link to date between vulnerability to schizophrenia and a known genetic anomaly.

Cognitive functioning in 22q11DS. Recent studies of the cognitive and educational abilities of children and adolescents with 22q11DS report significant impairment in intellectual ability, with a mean Full-Scale IQ around 70 (Bearden et al., 2001; Eliez et al., 2000; Lewandowski et al., 2007; Swillen et al., 2000). Early language delays have often been reported, although later cognitive deficits more closely resemble nonverbal learning deficits, including relative strengths in reading and verbal tasks (Swillen et al., 1999; Lewandowski et al., 2007), and relative weaknesses in visuo-spatial abilities, arithmetic, and object perception (Swillen et al., 1999; Swillen et al., 2000; Bearden et al., 2001; Henry et al., 2002). Children and adolescents with 22q11DS also tend to show a pattern of relative strengths in the areas of word knowledge, factual information, and understanding of concrete situations, and deficits in the areas of visual-spatial memory, non-verbal reasoning, and perceptual motor skills (Eliez et al., 2000; Swillen et al., 2000). Furthermore, recent findings suggest that nonpsychotic patients with 22q11DS exhibit specific deficits in prefrontally-mediated cognitive functioning including executive functioning, working memory, attention, and abstract and social thinking (Henry et al., 2002; van Amelsvoort et al., 2004; Lewandowski et al., 2007). Moreover, these deficits are not simply a function of general intellectual deficits, as they continue to account for significant variance over and above the effects of IQ (Bearden et al., 2004; Lewandowski et al., 2007).

Cognitive deficits in patients with 22q11DS do not appear to be related to the major physical anomalies associated with the syndrome (Bearden et al., 2001), as the same range of cognitive developmental outcomes is seen in children with and without cardiac defects and palate anomalies (Swillen et al., 2000). This finding suggests that deficits in intelligence and other delays are primarily associated with neurodevelopmental consequences of the 22q11 deletion itself, and are not secondary to physical manifestations or therapeutic interventions associated with the disorder (Shprintzen, 2000; Gerdes et al., 1999; Swillen et al., 2000).

Behavioral characteristics in 22q11DS. Studies of social and behavioral profiles in children and adolescents with 22q11DS have found elevations in social difficulties, and generally high rates of problem behaviors using observational and questionnaire data. Studies using the CBCL indicate that internalizing difficulties exceed externalizing difficulties, with elevations on the social problems, withdrawn, attention problems, and thought problems scales (Swillen et al., 1997; Swillen et al., 1999; Swillen, Devriendt, Ghesquiere, & Fryns, 2001). Additionally, a study of 2 to 18-year-olds reported that this pattern of elevations is conserved across age groups (Swillen et al., 1999). These findings are consistent with an earlier report based on observational and interview data by Golding-Kushner, Weller, and Shprintzen (1985), who found that children with 22q11DS exhibited “bland affect,” minimal facial expression, monotone voice, little disruptive behavior, and social problems that ranged from impulsivity to shyness. This pattern of behavioral and social characteristics is not merely reflective of behavioral profiles of children with low IQ and language difficulties. An investigation of behavior in 22q11DS

patients and children with low IQ and language disabilities without an identified genetic abnormality found that the 22q11DS patient group exceeded the comparison group on withdrawal, but were significantly lower than the comparison group on aggressiveness (Swillen et al., 2001).

As might be expected based on the social, behavioral, and cognitive difficulties of children with 22q11DS, patients exhibit increased rates of childhood psychopathology. Lewandowski et al. (2007) reported significantly more DSM-IV disorders in children with 22q11DS (62%) than in control participants (32%). Additionally, groups differed on ratings of Global Assessment of Functioning (Endicott, Spitzer, Fleiss, & Cohen, 1976), with control participants functioning significantly better overall. Despite the overall group differences in clinical diagnoses, there were no significant differences between the groups in terms of percentages of participants receiving mental health treatment (22q11DS group = 30%; control group = 28%). Commonly reported diagnoses in children with 22q11DS include AD/HD (most commonly inattentive type), phobia, depression, and autism spectrum disorders (Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2005; Lewandowski et al., 2007; Swillen et al., 1997), with rates of AD/HD, anxiety, and mood disorders as high as two to three times that of the general population (Murphy, 2002)

22q11DS, COMT, and schizophrenia. As noted above, the gene that codes for COMT maps to the commonly deleted region in people with 22q11DS (Grossman et al., 1992). As a result, patients with 22q11DS have only one copy of this gene. It is presumed that functional variation in enzyme activity based on the *Val*¹⁵⁸*Met*

polymorphism in people hemizygous for the COMT gene follows a similar pattern to that seen in non-deleted individuals. However, it is not clear the extent to which *Val*¹⁵⁸*Met* functionally alters enzyme activity in this population. That is, in people with two copies of the COMT gene, the Val/Val genotype is associated with a four-fold increase in COMT activity compared to people with the Met/Met genotype. The precise increase in enzyme activity in people with the Val/0 genotype compared with people with the Met/0 genotype has not been described. In addition to findings that indicate that 22q11DS is associated with cognitive impairment in general, and that deficits may be especially pronounced in prefrontally-mediated domains, a recent study of cognitive functioning within this population reported that Val-hemizygous patients performed significantly worse on prefrontally-mediated tasks compared to their Met-hemizygous counterparts (Bearden et al., 2004). However, both groups performed below the level that would be expected in a healthy population, with *z* scores on most tasks and on an executive function composite ranging from -0.5 to approximately -1.3 in the Met group, and less than -1.0 to approximately -1.6 in the Val group. This indicates that, while 22q11DS patients with the Met allele performed better than patients with the Val allele, both groups exhibited deficits compared to the tasks' normative samples. Since executive dysfunction has been associated with patients with schizophrenia, as well as with people identified as high-risk based on family history or psychometric identification, and since patients with 22q11DS exhibit highly elevated rates of psychosis in adulthood (although far less than 100%), the *Val*¹⁵⁸*Met* polymorphism may help refine identification of

patients with 22q11DS who are at especially elevated risk for the development of schizophrenia.

22q11DS as a genetic high-risk sample. Recent findings have suggested that the 22q11 deletion may provide a risk marker for schizophrenia and may even represent an etiologically specific subtype of the disorder (Bassett & Chow, 1999; Bassett et al., 1998, Gothelf et al., 1997; Murphy et al., 1999). Alternatively, 22q11DS may provide a more general contribution toward the neuromaldevelopment associated with vulnerability to schizophrenia, as the core clinical features of schizophrenia do not appear to differ between individuals with and without 22q11DS (Bassett et al., 2003). Furthermore, the medical consequences of 22q11DS may provide additional disruption of neurodevelopment. For example, perinatal hypoxia, which is associated with cardiac lesions found in 22q11DS, could contribute to the risk for schizophrenia (Cannon et al., 2000).

22q11DS provides a unique environment for the investigation of neurocognitive and genetic markers of vulnerability to schizophrenia and related disorders as patients have a strikingly increased risk for the development of psychosis, which is presumably influenced by the deletion of a specified 1.5 Mb genetic region. The location of the COMT gene within the commonly deleted region in 22q11DS, together with findings of increased schizotypy and schizophrenic-like neurocognitive deficits in persons with the Val/Val or Val/0 genotypes, suggests that this is a promising area for research into the relationship between COMT, 22q11DS, and risk for schizophrenia. It should be noted that there are a number of other genes in the commonly deleted region in 22q11DS that

have been associated with schizophrenia, which likely have complex interactions with COMT. While COMT and the *Val*¹⁵⁸*Met* functional polymorphism appear to be associated with prefrontal cognitive functioning, social and behavioral difficulties, and symptom measures associated with schizophrenia, it is likely that other genes and SNPs in the 22q11.2 region are associated with vulnerability to schizophrenia as well, either independently or in combination with COMT. Haplotype investigations such as those reported by Shifman et al. (2002) and Funke et al. (2005) may help identify combinations of alleles that are associated with vulnerability, and may help refine our understanding of the complex associations amongst these markers. Unlike most high-risk approaches to the study of schizophrenia, 22q11DS provides a clear genetic starting point for the investigation of indicators of vulnerability and their associations with genetic variation.

Goals and Hypotheses

The goal of the present study was to examine the relationship among schizophrenic-like neurocognitive functioning, social and behavioral dysfunction, and COMT genotype in a sample of children with 22q11DS. Studying children and adolescents permits the examination of psychopathology and schizophrenic-like cognitive and behavioral deficits absent the consequences of schizophrenia, such as medication effects, hospitalization, or stigma, and ultimately allows for the prospective study of risk. It is hypothesized that a) 22q11DS participants with the Val allele will perform worse on neurocognitive measures of prefrontal functioning than 22q11DS participants with the Met allele, but will not differ on non-prefrontal measures, b) participants with the Val allele will exhibit more behavioral dysfunction consistent with those identified in

children who later develop schizophrenia than participants with the Met allele, c) participants with the Val allele will exhibit more psychopathology than participants with the Met allele, especially in domains associated with reduced executive control such as AD/HD while participants with the Met allele will exhibit more psychopathology in mood and anxiety domains, and d) the COMT haplotype described by Shifman et al. (2002) will be associated with both schizophrenic-like neurocognitive deficits and with psychosocial difficulties that have been associated with schizophrenia and schizotypy. This study represents the first work to date to examine the effects of a COMT haplotype on neurocognitive functioning and psychopathology in nonpsychotic 22q11DS patients.

Hypothesis 1: Patients with the Val allele will perform worse than patients with the Met allele on measures of sustained attention, working memory, and executive functioning. The two groups will not differ significantly on measures of general intelligence or achievement, or on a task of verbal learning and memory. It was predicted that 22q11DS patients with the Val allele would perform worse than 22q11DS patients with the Met allele on tasks that are believed to tap prefrontal functioning, but not on tasks that measure general fund of knowledge, academic achievement, or verbal learning. It should be noted that the average IQ of children with 22q11DS is approximately 70, which is two standard deviations below the mean for the general population. Thus, while 22q11DS patients with the Val allele were hypothesized to perform worse than their Met allele peers, all children are expected to exhibit deficits in cognitive functioning in all domains assessed, including intelligence, academic achievement, sustained attention, working memory, and verbal learning.

Hypothesis 2: Patients with the Val allele will exhibit higher rates of behavioral and social difficulties than patients with the Met allele in terms of social isolation and withdrawal. Patients with the Met allele will exhibit increased levels of internalizing difficulties such as anxiety and affective problems. Participants with the Val allele are expected to exhibit deficits similar to those seen during premorbid development in patients who later develop schizophrenia. Conversely, patients with the Met allele are expected to exhibit more difficulties in areas of affective dysregulation, including anxiety and depression. As with cognitive measures, all participants were expected to exhibit difficulties socially and behaviorally. As noted above, patients with 22q11DS often have medical difficulties that limit exertion and increase days in the hospital and away from peers, facial dysmorphologies, intellectual deficits and learning difficulties, and speech disorders, each of which may affect children's behavior and social interactions. Additionally, these difficulties would be expected to increase anxiety and affective dysregulation in patients. However, within the 22q11DS group, it was predicted that patients with the Val allele would exhibit schizophrenic-like behavioral and social dysfunction such as social isolation, while patients with the Met allele would exhibit increased affective dysregulation.

Hypothesis 3: Patients with the Val allele will exhibit higher rates of psychopathology than patients with the Met allele, specifically in areas that appear to be associated with deficits in prefrontal functioning, and greater deficits in global functioning. Patients with the Met allele will exhibit more mood and anxiety symptoms than patients with the Val allele. It was predicted that participants with the Val allele

will exhibit greater deficits in global functioning compared to their peers with the Met allele. Additionally, it was predicted that the Val group would exhibit especially high rates of AD/HD, Oppositional Defiant Disorder, and conduct problems, which are associated with poor planning, poor working memory, or decreased behavioral inhibition. AD/HD has been hypothesized to be associated with difficulties in sustained attention, planning and sequencing, and behavioral inhibition – tasks that it was hypothesized the Val group would exhibit deficits on compared to the Met group. Patients with the Met allele were hypothesized to exhibit greater symptoms of mood and anxiety disorders than patients with the Val allele, consistent with findings that the Met allele is associated with hyperresponsivity to negative stimuli in adults.

Note that, while the incidence of psychotic disorders appears to be significantly elevated in adults with 22q11DS, psychosis was a rule-out criterion for recruitment into this study, as we are hoping to examine vulnerability to psychosis rather than correlates of the disorder itself. Furthermore, early premorbid manifestations of vulnerability for schizophrenia typically do not involve positive symptoms of schizophrenia, but rather neurocognitive and behavioral manifestations. Thus, we did not expect to find group differences in rates of psychotic disorders at this stage in the investigation. However, longitudinal follow-up of our participants is planned and we expect to see psychotic disorders emerge in a subset of our participants as they enter adolescence and adulthood.

Hypothesis 4: Patients with the COMT haplotype described by Shifman et al. (2002) will exhibit more neurocognitive deficits and more psychopathology than patients without the COMT haplotype. The COMT haplotype described by Shifman et al. (2002),

which includes the Val allele, was found to be more predictive of schizophrenia than the *Val*¹⁵⁸*Met* polymorphism alone. Additionally, recent reports have suggested that this haplotype is also associated with bipolar disorder – another disorder that may be over-represented in patients with 22q11DS. However, as of the writing of this paper, this haplotype has not been examined in patients with 22q11DS, or in a high-risk group of nonpsychotic individuals. Since the genotype involves polymorphisms in the COMT region, COMT has been associated with prefrontal cognitive performance, and people identified as at-risk for the development of psychosis perform worse than control participants on prefrontally-mediated tasks, it was hypothesized that children with this haplotype will both perform worse on prefrontally-mediated cognitive tasks and will exhibit more psychopathology than children without the haplotype.

CHAPTER II

METHOD

Participants

The sample consisted of 27 patients with 22q11DS recruited through the Department of Genetics at Wake Forest University School of Medicine (WFUSM). Investigations of the COMT polymorphism and neurocognitive and behavioral symptoms in children with 22q11DS have detected group differences with sample sizes similar to that of the present study (Bearden et al., 2004; Bearden et al., 2005), and pilot work from our lab suggests that the present sample is sufficient. In previous samples of participants without a 22q11 deletion (e.g. Bruder et al., 2005; Malhotra et al., 2002) approximately 17% of participants had the Met/Met genotype, 44% had the Val/Met genotype, and 38% had the Val/Val genotype, which represents allele frequencies of approximately 39% Met and 61% Val. This is consistent with findings of allele frequency in samples of participants with 22q11DS (Bearden et al., 2004; Bearden et al., 2005). Therefore, it was expected that these proportions would be approximately the same in the present sample of patients with 22q11DS. Indeed, the allele frequency in the present sample was 48% Met and 52% Val, $X^2 = 1.88$, ns, which is consistent with previous findings and indicates that the present sample is representative of the general population and patients with 22q11DS in terms of allele distribution.

The Val and Met groups did not differ on age at assessment, level of education, ethnicity, sex, parental SES, or global adjustment (see Table 1). All participants were recruited by a Medical Geneticist and a Licensed Genetics Counselor and were seen in the Pediatric Medical Genetics clinic at WFUSM as part of ongoing treatment associated with the 22q11DS. 22q11.2 deletions were confirmed using fluorescence *in situ* hybridization (FISH). All patients of the Genetics Clinic between the ages of 6 and 16 with an identified 22q11 deletion were invited to participate in the study. Consent was obtained from the parent or legal guardian of each participant.

Materials

Neurocognitive measures evaluating sustained attention, executive functioning, verbal working memory, intelligence, and achievement were administered. Sustained attention was assessed using the Continuous Performance Test (CPT; Cornblatt, Lenzenweger, & Erlenmeyer-Kimling, 1989), executive functioning was assessed using the Wisconsin Card Sorting Test (Heaton et al., 1993), and verbal working memory was assessed using the California Verbal Learning Test-Children's Version (CVLT-C; Delis, Kramer, Kaplan, & Ober, 1994). Intelligence was measured using the Wechsler Intelligence Scale for Children, 3rd and 4th Editions (WISC-III; Wechsler, 1991; WISC-IV; Wechsler, 2003), and academic achievement will be measured using the Wechsler Individual Achievement Test, 2nd Edition (WIAT-II; Wechsler, 2001). Research on cognitive deficits in individuals with schizophrenia and schizotypal personality disorder and people identified as at-risk based on psychometric identification or first-degree relative status have found deficits in attention, executive functioning, and verbal working

memory using these measures or comparable adult versions (Aloia et al., 1996; Bergman et al., 1998; Cornblatt & Erlenmeyer-Kimling, 1985; Cornblatt et al., 1988; Erlenmeyer-Kimling et al., 2000; Erlenmeyer-Kimling, 2000; Gold & Harvey, 1993; Gooding, Kwapil, & Tallent, 1999; Lenzenweger & Dworkin, 1998; Lyons et al., 1995; Nuechterlein, 1983; Saykin et al., 1991). Behavioral functioning was assessed using the Child Behavior Checklist (CBCL; Achenbach, 2001), and social functioning was assessed using the Social Skills Rating Scale (SSRS; Gresham & Elliot, 1990). Childhood psychopathology was examined using the Computerized Diagnostic Interview Schedule for Children (C-DISC; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000).

Continuous Performance Test. The CPT assesses the ability to focus and sustain attention (Cornblatt et al., 1988). Participants were assessed with the Identical Pairs (IP) and AX versions of the test. In the CPT-IP, participants were presented with a series of numbers or shapes on a computer screen, and instructed to lift their fingers off a computer mouse if they saw identical stimuli appear on consecutive trials. Participants were tested on four IP conditions involving numbers or shapes, and stimuli which were presented “fast”, meaning that they appeared for less time on the screen (50ms), or “slow” meaning that they appeared for more time on the screen (150ms). The AX version involved the presentation of single digits on the screen. Participants were instructed to lift their fingers off the mouse button when they saw the number eight immediately preceded by the number two. In addition to assessing attention, the AX version also taps the ability to gate or inhibit incorrect responses. Prior to the first IP condition and the AX condition, participants completed a practice session using cards.

This allowed participants to become familiar with the types of stimuli they would be encountering, and allowed the experimenter to determine whether or not participants understood the instructions. Participants then completed a practice session on the computer, followed by the test sessions. Scores were reported in terms of d' , a signal detection index that is relatively unaffected by response bias (i.e. over- or under-responding). The four CPT-IP conditions were combined to form a single CPT-IP composite score. The CPT has been normed for use with individuals from a wide range of ages and ability levels and reports good reliability (Cornblatt et al., 1988; Heaton et al., 1993). Cornblatt et al. (1985) found that the CPT-IP was an effective predictor of the development of schizophrenia in a genetically at-risk sample.

The Wisconsin Card Sorting Test. The WCST is widely used to assess executive functioning (Chelune & Baer, 1986). Participants viewed four cue cards on a computer screen containing one to four colored shapes that matched keyboard stickers placed on four adjacent computer keys. Participants also saw a single card that they were to match to one of the four cue cards. At each turn the correct matching rule may be color, number, or shape, with only one of the categories being correct per trial. The participant was instructed to match the card to one of the four cue cards, but was not told the correct matching rule. Participants were given both visual and auditory feedback (either RIGHT or WRONG). The participant must incorporate the feedback from each turn to correctly place the next card. The sorting rule (color, number, or shape) changed after ten consecutive correct responses without the participant's knowledge, requiring him or her to apply a different sorting rule. Indices used in the present study include perseverative

errors, or failure to switch sorting rules despite feedback indicating that the old rule is no longer effective, nonperseverative errors, and conceptual level response, an indicator that an understanding of the sorting rule has been achieved. Patients with schizophrenia and individuals presumed to be at risk for schizophrenia exhibit deficits on WCST performance (e.g., Goldberg & Weinberger, 1988; Gooding et al., 1999).

The California Verbal Learning Test-Children's Version. The CVLT-C is a test of verbal learning and memory designed to assist in the identification of impairments associated with, or secondary to, learning disorders and neurological and psychiatric problems in children aged 5 to 16 years. This measure was developed and normed for use with children, and has good reliability and validity (Delis et al., 1994). Lists of words presented as shopping lists were read aloud, and participants were asked to recall as many words as possible. The first list (List A) consisted of 15 words, each belonging to one of three semantic clusters – fruits, clothing, and playthings. The list was read once and the participant was asked to recall as many words as he or she could. List A was repeated four more times, with recall assessed after each trial. Next, a distracter list (List B) was read, consisting of 15 new words, each belonging to one of three semantic clusters, one of which was the same as List A (fruits), and two of which were new (sweets and furniture). The participant was asked to recall as many words from List B as he or she could. The participant was then asked to recall as many words from List A as possible. This task was followed by a cued-recall task in which the participant was asked to recall as many words from List A as possible within each of the three semantic clusters. The participant was then given a twenty-minute break during which a non-verbal task (WCST) was

performed. Following this long delay, the participant was asked to perform both free-recall and cued-recall tests of List A. Finally, a recognition task was administered in which a list of 45 words was read. The participant was asked to respond affirmatively only when he or she heard a word from List A. The word list consisted of words from List A, words from List B, and previously untested words, some of which were semantically related to the clusters from List A and B.

The CVLT-C produces a number of indices that can be grouped into the broad domains of recall, learning strategies, and recognition. In the present study, recall was measured using scores from the five immediate recall trials for list A, the number of words correct on the first list A trial, and scores on the short-delay and long-delay free and cued recall conditions. Learning strategies were evaluated using semantic and serial clustering scores, with semantic clustering indicating a more advanced learning style. Lastly, recognition was examined using scores from the recognition task. Comparisons between recognition and recall can be made in order to evaluate whether problems with verbal memory are at the level of encoding or retrieval. For example, low scores on recall tasks followed by a relatively higher score on the recognition task may be indicative of a retrieval problem, as the words are apparently encoded properly. However, poor scores on recall and recognition may indicate an encoding problem, as the words are not recognized, even with prompting. While there is no literature to date examining the relationship between CVLT-C performance and schizotypy in children, patients with schizophrenia exhibit impairment on verbal learning tasks, as do adults with schizotypal personality disorder (Bergman et al., 1998; Hill, Beers, Kmiec, Keshavan, &

Sweeney, 2004). However, as noted above, children with 22q11DS tend to show relative strengths in verbal, as opposed to nonverbal, performance.

The Wechsler Intelligence Scale for Children, 3rd and 4th Editions. The WISC-III and the WISC-IV are widely used intelligence tests for children. The WISC-III battery consists of ten subtests that produce individual scaled scores and combine to yield a Verbal IQ score, a Performance IQ score, and a Full-Scale IQ score. The mean for Verbal IQ, Performance IQ, and Full Scale IQ is 100 with a standard deviation of 15. Additionally, two extra subtests can be administered and combined with the 10 basic subtests to yield four factor scores, including Verbal Comprehension, Perceptual Organization, Freedom from Distractibility, and Processing Speed. These scores are also based on a mean of 100 and a standard deviation of 15. The WISC-IV consists of ten subtests that yield a Full Scale IQ score and four scale scores: Verbal Comprehension, Perceptual Organization, Processing Speed, and Working Memory. While the WISC-III and WISC-IV scale scores are not made up of identical subtests, the Verbal Comprehension scale is comparable to Verbal IQ ($r = .87$), the Perceptual Organization scale is comparable to Performance IQ ($r = .74$), and the Full Scale IQ scores from the two tests are comparable ($r = .89$) (Wechsler, 2003). Participants assessed after January, 2004 were administered the WISC-IV, while prior to 2004 participants were administered the WISC-III. While it would have been preferable to maintain use of the WISC-III throughout data collection, the benefit of providing useful psychoeducational testing reports to families was a major incentive to participant recruitment. Together with the

comparability of the two versions of the test, it was decided that use of the current version of the WISC was appropriate.

The Wechsler Individual Achievement Test, 2nd Edition. The WIAT-II is a widely used test of academic achievement. The present study employed six subtests that assess word reading, phonetic decoding, and reading comprehension in the domain of Broad Reading, computational skills and math reasoning in the domain of Broad Mathematics, and spelling achievement. The testing yields scaled scores on each of the subtests and the broad domains. These scores are normed to a mean of 100 and a standard deviation of 15.

Computerized Diagnostic Interview Schedule for Children. The C-DISC is a semi-structured interview that was administered to each participant's parent or primary caregiver in order to assess psychopathology in the participant. The C-DISC is based on the DSM-IV (American Psychiatric Association, 2001) criteria for mental disorders, and is designed to address specific symptoms that must be evaluated in order to determine diagnostic status. The interview contains a number of modules that assess most disorders described by the DSM-IV. The present study assessed Mood Disorders, Anxiety Disorders, Psychotic Disorders, Attention Deficit /Hyperactivity Disorder (AD/HD), Oppositional-Defiant Disorder, and Conduct Disorder. None of the parents reported that their children used substances; therefore, the substance use disorders modules were not administered.

The Child Behavior Checklist. The CBCL is a 118-item questionnaire designed to tap childhood functioning across a wide array of areas, including competencies and

specific behavioral and emotional problems in children and adolescents ages 6-18.

Questionnaires are completed by a parent, guardian, or close relative of the child who knows him or her well. Items are keyed as 0 (not true), 1 (somewhat or sometimes true), or 2 (very true or often true) based on the respondent's knowledge of the child currently or within the past 6 months. Items are entered into a computer scoring software package that generates T-scores, with a mean of 50 and a standard deviation of 10. The scales that are generated include: Activities, Social, School, and a Total Competency score within the Competency domain, and Withdrawn, Somatic, Anxious/Depressed, Social, Thought Problems, Attention, Delinquent, Aggressive, Internalizing, Externalizing, and a Total Problem score within the Problem domain.

Scores from the CBCL have been used to measure functioning in children with an array of psychiatric disorders, and have been associated with premorbid behavioral difficulties in children who later develop schizophrenia. A study of 23 adolescents with early onset schizophrenia found that children who went on to develop psychosis in adolescence exhibited higher problem scores on the CBCL compared to healthy children, and specific deficits in social competencies and school problems when compared to adolescents with anorexia nervosa (Muratori, Salvadori, D'Arcangelo, Viglione, & Picchi, 2005). Additionally, early and persistent behavioral problems through childhood as measured by the CBCL have been associated with more severe symptoms in adult patients with schizophrenia based on retrospective report (Rossi et al., 2002). In first-degree relatives, scores on the CBCL have been associated with later development of psychosis. In particular, high scores on the withdrawn, delinquent, and aggressive

behavior scales in nonpsychotic adolescents predicted onset of schizophrenia during adulthood (Miller, Byrne, Hodges, Lawrie, & Johnstone, 2002).

The Social Skills Rating Scale. The SSRS is a questionnaire measure that assesses social functioning including social skills and problem behaviors in children and adolescents ages 3-18. The competency scales measure behaviors in the domains of Cooperation, Empathy, Assertion, Self-Control, and Responsibility, while the problem scales assess behaviors that interfere with appropriate social functioning and development, including aggression and poor temper control (Externalizing), sadness and anxiety (Internalizing), and fidgeting and impulsive acts (Hyperactivity). Raw scores are provided on the subscales, and standardized scores are generated for the scale scores based on means of 100 and standard deviations of 10. Standardized scores are calculated based on separate norms for boys and girls.

Genotyping. The COMT genotype was determined by restriction fragment length polymorphism (RFLP). A 109 base pair polymerase chain reaction product was obtained in 30-40 cycles with an annealing temperature of 55°C with the use of primers 5'-CTCATCACCATCGAGATCAA and 5'-CCAGGTCTGACAACGGGTCA described in detail by Lachman et al., 1996. The Val and Met alleles were discriminated by digesting the PCR product with *Nla*III at 37°C overnight and separated by agarose gel electrophoresis (3.5 - 4%). The Val allele (uncut) was identified by digestion products at 87 and 22 base pairs, while the Met allele (cut) was identified by digestion products at 69, 22, and 18 base pairs. These analyses were conducted at WFUBMC by a molecular geneticist or advanced lab technician experienced in PCR.

Procedure

Participants were assessed individually at Wake Forest University Baptist Medical Center and the University of North Carolina at Greensboro Department of Psychology. DNA was collected through blood draw or sputum collection, which was performed by a pediatrician. The neurocognitive measures and interviews were administered by a licensed clinical psychologist or trained graduate students in clinical psychology under the supervision of a licensed clinical psychologist. The administration of the assessment battery requires approximately 4 to 5 hours, so the testing was broken up into two or three sessions to minimize the effects of participant fatigue on the assessment results. In the event that a participant was assessed using the WISC-III, WISC-IV, or WIAT-II within the past year, the results from the previous assessments were obtained. Control participants received \$50 upon the completion of the testing sessions. Additionally, all participants received summary reports of their assessment results.

CHAPTER III

RESULTS

Hypothesis 1: Neurocognitive and Intellectual Functioning

The Val and Met groups were compared on measures of sustained attention, working memory, executive functioning, verbal learning, intelligence, and academic achievement using *t*-tests. Additionally, effect sizes were calculated using Cohen's *d*. Cohen's *d* measures the magnitude of an observed effect in units of standard deviation independent of sample size, providing a complement to statistical significance testing. According to Cohen (1988), $d = .2$ indicates a small effect size, $d = .5$ indicates a medium effect size, and $d = .8$ indicates a large effect size. Group means, comparisons, and effect sizes on the CPT, WCST, and CVLT-C are reported in Table 2. Groups did not differ significantly on any of the CPT indices. However, the effect size analyses of the CPT-IP scores showed a moderate effect of genotype on performance with the Val group performing better ($d = -.57$). Conversely, a moderate effect of genotype on CPT-AX performance was found, with Met participants performing better ($d = .60$). It should be noted that both groups performed near the floor on the CPT-IP, suggesting that the difficulty of the task may have been too great for the subjects. No group differences were

found on the WCST indices, and effect sizes were small. Finally, groups did not differ on any of the CVLT-C indices, and effect sizes were small at best.

Group means, comparisons, and Cohen's d scores on the WISC are summarized in Table 3. The Met group scored significantly higher than the Val group in terms of Full Scale IQ ($t = 2.19, p < .05; d = .86$) and Verbal IQ scores ($t = 2.18, p < .05; d = .86$), but did not differ on the Performance Scale scores. Groups differed on the Working Memory and Processing Speed factor scores, with the Met group performing significantly better than the Val group ($t = 2.40, p < .05$ and $t = 2.09, p < .05$, respectively). Comparisons on these measures indicated large effect sizes for both the Working Memory and the Processing Speed factors ($d = 1.0$ and $.85$, respectively). Finally, in terms of subtest scores, the Met group performed significantly better than the Val group on Symbol Search ($t = 2.36, p < .05$) and Picture Arrangement ($t = 3.56, p < .01$), and showed trends in the same direction on the Arithmetic and Picture Completion subtests ($t = 1.98, p < .10$ and $t = 1.94, p < .10$, respectively). Furthermore, the Symbol Search, Arithmetic, Picture Completion, and Picture Arrangement subtests showed large effect sizes, and the Similarities, Vocabulary, Information, and Digit Span subtests showed moderate effect sizes.

Scores from the WIAT-II are presented in Table 4. The six subtests administered and the Broad Reading and Broad Math Clusters were examined. Groups did not differ significantly on the Broad Reading Cluster, any of the reading subtests, or the Spelling subtest. However, the Met group scored significantly higher than the Val group on the Math Reasoning subtest ($t = 2.78, p < .05$), and showed a trend toward higher scores on

the Broad Mathematics Cluster ($t = 1.96, p < .10$). In terms of effect size, examination of the Math Reasoning subtests indicated that there was a large group effect, and moderate group effects were found on the overall Broad Reading Cluster, the Word Reading and Reading Comprehension subtests, the Spelling subtest, the Broad Mathematics Cluster, and the Numerical Operations subtest.

Hypothesis 2: Social and Behavioral Functioning

Scores from the CBCL Competency and Problem Scales are presented in Table 5. The overall Competency Total score, the overall Problem Total score, and the ten problem subscale scores were compared using t -tests. The Val group exhibited higher problem scale scores on the Anxious/Depressed and Aggressive scales, but did not differ from the Met group in terms of Competency, Total Problems, or any of the other problem scores. However, a moderate effect size was found on the Total Competency score, with the Val group scoring lower in total competency. Moderate effect sizes were also found on the Withdrawn, Internalizing, and Externalizing problem subscales, with the Val group exhibiting higher problem ratings.

Measures of social functioning based on SSRS ratings are presented in Table 6. T -tests showed that patients with the Val allele were rated lower than patients with the Met allele on Assertion ($t = 3.23, p < .01$), and showed a trend toward poorer functioning based on the Total Skills composite ($t = 1.74, p < .10$). Additionally, a large group effect size was found on the Assertion subscale and moderate effect sizes were found on the Responsibility and Skills Total scales. No differences were found on the Externalizing, Internalizing, Hyperactivity, or Total Problem scales.

Hypothesis 3: Childhood Psychopathology

Val and Met groups were compared on measures of psychopathology based on scores on the C-DISC interview (see Table 7). Overall functioning was examined using the GAF. Participants' scores were recorded dichotomously for each disorder (present or absent) except for AD/HD, which was recorded both dichotomously and continuously based on inattention symptom count and hyperactivity symptom count. Groups were compared using Fisher's Exact Test for percentage of participants who met criteria for a given disorder, any anxiety disorder, and any mood disorder. Additionally, groups were compared using *t*-tests on measures of AD/HD symptoms, and on GAF scores. Groups did not differ on any measure of psychopathology, AD/HD symptoms, or overall adjustment as measured by the Global Assessment of Functioning (Table 1).

Hypothesis 4: Haplotype Analyses

One 3-allele haplotype and three 2-allele haplotypes were described by Shifman et al. (2002). The 3-marker haplotype included *Val*¹⁵⁸*Met*, and the closely-linked rs737865 and rs165599 loci. In all combinations of 2-marker haplotypes, as well as in the 3-marker haplotype, the G allele was found to be associated with risk for schizophrenia. Individual genotype profiles were examined, and those patients who had a G-G or G-G-G haplotypes were considered haplotype-positive. Seven of the 21 patients for whom data was available for all three loci were haplotype-positive – six patients were positive for a 2-marker haplotype, and one patient was positive for the 3-marker haplotype. By comparison, haplotype examination of 19 control participants previously reported on (e.g. Lewandowski et al., 2007) for whom complete genetic data was

available showed that none had either a 2-marker or the 3-marker haplotype, Fisher's Exact Test = .009. Four patients had the COMT-rs165699 G-G haplotype, two patients had the COMT-rs737865 G-G haplotype, and one patient had the COMT-rs165599-rs737865 G-G-G haplotype. No patient had the rs737865-rs165599 G-G haplotype.

Patients who were haplotype-positive were compared with patients who were haplotype-negative on measures of neurocognitive performance, IQ and achievement scores, and psychopathology. Examination of cognitive functioning in patients with the 2- and 3- marker haplotypes showed that haplotype-positive patients scored significantly worse on WCST non-perseverative errors ($t = -3.18, p < .01$), percent conceptual level response ($t = -2.95, p < .01$), and a showed a trend toward fewer categories completed ($t = -2.04, p < .10$) (see Table 8). There were no significant group differences on any of the CVLT-C indices, or on the CPT-IP or CPT-AX measures based on t - test. However, effect size analyses indicated that there was a small to moderate effect size in terms of CPT-AX scores in the expected direction (Cohen's $d = -.47$). Surprisingly, a moderate effect size was found in the opposite direction in terms of CPT-IP performance, with haplotype-negative patients performing worse than haplotype-positive patients (Cohen's $d = .54$). No significant differences emerged between groups in terms of CVLT-C functioning; however, moderate effect sizes were found on the Short Delay Free recall and the Long Delay Cued recall conditions, with haplotype-positive patients performing worse.

Means and standard deviations from IQ and achievement testing are presented in Table 9. In terms of IQ Scale scores, patients who were haplotype-positive exhibited

trends toward lower Full Scale IQ ($t = -2.03, p < .10$) and Verbal IQ ($t = -1.89, p < .10$). Patients who were haplotype-positive performed worse on the Working Memory and Processing Speed factors ($t = -2.45, p < .05$ and $t = -2.32, p < .05$, respectively), and showed a trend toward poorer performance on the Perceptual Organization factor ($t = -1.90, p < .10$). Large effect sizes were observed on the Full Scale IQ score, Verbal IQ score, all four Factor scores, and several of the subtests, including Digit Span, Coding, Vocabulary, Symbol Search, Arithmetic, Picture Completion, and Picture Arrangement. Additionally, moderate effect sizes were observed on the Performance IQ Scale score and most of the remaining subtests, including Similarities, Comprehension, and Information. The only subtests that showed small effects were Block Design and Object Assembly. All group differences were in the expected direction, with haplotype-positive patients scoring worse than haplotype-negative patients. In terms of academic achievement testing with the WIAT-II, haplotype-positive patients scored significantly lower than haplotype-negative patients on the Numerical Operations subtest, and showed trends toward poorer scores on the Math Reasoning subtest and the Broad Mathematics Cluster. Effect size analyses showed large effects of group on the Broad Mathematics Cluster, and the Numerical Operations and Math Reasoning subtests. A moderate effect size was found on the Word Reading subtest. Again, all group differences were in the expected direction, with haplotype-positive patients scoring worse than their haplotype-negative peers.

Scores from the CBCL and SSRS by group are presented in Tables 10 and 11.

Haplotype-positive patients scored significantly lower on the CBCL Total Competency (t

= -2.79, $p < .05$) and on the SSRS Assertion scale ($t = -2.97, p < .01$). Again, due to the small sample size in the haplotype-positive group, effect sizes were calculated in order to examine group differences on behavioral and social measures. Large group effects were seen on the CBCL Competency scale and the SSRS Assertion scale, and moderate effect sizes were seen on the CBCL Withdrawn and Anxious/Depressed scales and on the SSRS Skills Total scale.

Finally, descriptive information is provided separately for the one patient who was positive for the 3-marker haplotype described by Shifman et al. (2002) (Tables 12 and 13). In terms of cognitive functioning, this patient scored in the borderline mentally-retarded range based on the WISC Full Scale IQ score, VIQ, and PIQ scores. These scores are commensurate with the means within the 22q11DS patient group as a whole. In terms of WIAT-II scores, this participant scored more than one standard deviation below the mean on the Broad Reading cluster, and more than two standard deviations below the mean on the Broad Math cluster. Again these scores are commensurate with 22q11DS group means. In terms of sustained attention and verbal learning and memory, this patient's scores were more than one standard deviation below the 22q11DS group as a whole on the CPT-IP measure, and showed a trend in the same direction on the CPT-AX measure. Additionally, the patient scored at least one standard deviation below the 22q11DS group on most of the CVLT-C indices. Finally, in terms of social and behavioral functioning, this participant's scores on the CBCL Withdrawn and Anxious/Depressed scales were more than one standard deviation above the 22q11DS group (indicating poorer functioning in these domains). Conversely, this patient's score

on the Attention problem scale was greater than one standard deviation below the 22q11DS mean (indicating fewer attention problems).

CHAPTER IV

DISCUSSION

The present study examined the relationship of the COMT *Val*¹⁵⁸*Met* polymorphism with neurocognitive functioning and childhood psychopathology in a sample of children and adolescents with 22q11DS. It was hypothesized that prefrontally-mediated cognitive functioning would be associated with genotype, with Val patients performing worse on tasks of executive functioning, working memory, and sustained attention than patients with the Met allele. Additionally, it was hypothesized that genotype would not be associated with general intelligence or academic achievement, or performance on a nonprefrontally-mediated task of verbal learning and memory. Furthermore, it was predicted that children with the Val allele would be more likely to exhibit social and behavioral deficits associated with vulnerability to psychosis, and psychopathology associated with deficits of prefrontal control such as AD/HD and conduct problems. It was further hypothesized that children with the Met allele would be more likely to exhibit psychopathology associated with hyperresponsivity to negative affect, such as mood and anxiety disorders. Findings indicated that the COMT *Val*¹⁵⁸*Met* polymorphism was associated with overall intellectual and academic functioning, and with deficits in working memory. Additionally, the COMT *Val*¹⁵⁸*Met* polymorphism was associated with social and behavioral functioning in children with 22q11DS. While the present sample was not large enough to permit the examination of the effects of sex or

age on cognitive and behavioral functioning, group differences do not appear to be a function of sex or age as the groups did not differ on these variables. The present study represents a preliminary investigation of the effects of a genetic variant on cognitive and behavioral functioning in children with a putative genetic vulnerability to schizophrenia. Additionally, this is the first study to date to examine a previously-reported COMT susceptibility haplotype in patients with 22q11DS.

Cognitive Performance and COMT Genotype

Comparisons of COMT genotype in patients with 22q11DS on measures of cognitive functioning indicated that, as expected, patients with the Val allele exhibited deficits on tasks measuring working memory and processing speed. While significant differences were not detected on measures of sustained attention and executive functioning, the small sample size and moderate to large effect sizes on several indices suggest that the present study was underpowered to detect such differences in younger children. In terms of intellectual functioning and academic achievement, patients with the Met allele scored higher on the Math Reasoning subtest of the WIAT-II. Additionally, moderate effect sizes were found on many of the WISC factors and subscales, and on all measures of the WIAT-II except pseudoword decoding. Children with the Val allele on average performed significantly below standardized norms on all subtests and both available cluster scores of the WIAT-II, whereas children with the Met allele on average were not significantly below standardized norms in terms of Broad Reading, each of the reading subtests, and the spelling subtest. In terms of verbal

learning and memory, groups did not differ on any index of the CVLT-C, indicating that these domains of functioning are not affected by COMT genotype.

Group differences in terms of intelligence and academic achievement were not anticipated. It is possible that, in patients with 22q11DS, the Met allele may be a marker of better overall cognitive functioning rather than better prefrontal functioning specifically. This is consistent with findings of Barnett et al. (2007), who reported that COMT may have an effect on IQ variation. However, the WISC Scale Scores are comprised of clusters of individual subtests which tap different aspects of intellectual functioning. Children with the Val allele performed significantly worse than children with the Met allele on several subtests, and had mean scores that were observationally lower on each subtest. While many of these differences were not statistically significant, they were combined to yield Factor and Scale Scores that were significantly different. Specifically, the factor scores from the WISC the showed the greatest group differences were the Working Memory and Processing Speed factors, indicating that, while overall IQ was lower in children with the Val allele, scores on the subtests that make up these two factors may have been especially impaired.

The subtest that showed the greatest group difference was Picture Arrangement – a task that requires children to arrange cards in an order that tells a logical story. This task requires attention to visual detail, social reasoning, cognitive flexibility, and working memory skills, as the task is facilitated by the ability to hold the content of the cards in memory and manipulate them in order to find the correct story. Additionally, this task is timed, such that quicker correct solutions yield more points, making processing speed an

important component as well. It should be noted that the group differences on this task do not appear to be a result of children with the Met allele performing especially well, but, rather, that children with the Val allele performed especially poorly. The mean of the Met group on this task was 6.1 ($sd = 2.4$), while the mean of the Val group was 2.8 ($sd = 1.6$). When the subtest scores were averaged within groups, the mean subtest score across all subtests for the Met participants was 6.4 ($sd = .67$) and the mean subtest score for the Val participants was 4.6 ($sd = .95$). Thus, the Met group's scores on Picture Arrangement were commensurate with their scores in general, while the Val participants appear to have performed more poorly than would be expected based on their other scores, and showed a marked deficit compared to children in the general population, falling more than two standard deviations below the mean.

Thus, while Full Scale and Verbal IQ scores differed between groups, there were specific domains of cognitive functioning that influenced these scores, including tasks that tap reasoning, working memory, and visual attention and processing speed. While scores on tasks that tap general fund of knowledge such as information and Vocabulary also showed moderate effect sizes by group, these effect sizes were smaller, and were not significantly different. Together, these findings suggest that patients with the Val allele exhibit general deficits in intellectual functioning, but more profound deficits in the domains of working memory and processing speed.

Again, it was surprising that genotype did not appear to affect executive functioning as assessed by the WCST, and showed a moderate effect size in the opposite direction expected on the CPT-IP. While it is possible that genotype does not affect

cognitive processing on the WCST, it is also possible that the children with 22q11DS in our sample were too young and/or cognitively compromised for significant group differences on these measures of prefrontal functioning to emerge. Similarly, scores on the CPT-IP indicate that this task may also have been too difficult for children with 22q11DS. Within the 22q11DS group, d' scores for both Val and Met groups were close to zero on all IP conditions, suggesting that neither group exhibited an adequate level of ability to meet the demands of the tasks. Additionally, scores on the WCST and CPT-IP were not correlated with any other measure of cognitive functioning or academic achievement, suggesting that this measure is not tapping cognitive processes associated with any index of the WISC or the WIAT. Thus, there may be a floor effect that is being observed within the 22q11DS group on these measures.

Scores on the WISC and WIAT, assessment tools that are designed to detect a wide range of functioning and ability in children, may have been better suited to this sample in terms of detecting variability at the lower range of functioning. Indeed, differences within the 22q11DS group were detected in several domains using these measures, and patterns of deficits in the Val group were in the domains that were expected. These findings lend support to the possibility that the present assessments selected for executive functioning and sustained attention were not sensitive enough to detect variation in functioning at the lower end, as it would seem improbable to find deficits in general intellectual ability that are not accompanied by impairment in prefrontal cognitive functioning. That is, if the Val allele is associated with poorer general intellectual functioning, it would be expected that it would also be associated

with poorer cognitive functioning in prefrontal domains. Additionally, it should be noted that, due to the small sample size, the present study may not have had enough power to detect differences.

It is important to note that, as a group, children and adolescents with 22q11DS perform poorly compared to healthy children on assessments of general intellectual ability and academic achievement, and on tasks of executive functioning and sustained attention. This is based on normative data for these tasks, and previous work that has demonstrated that children with 22q11DS exhibit deficits in intellectual functioning and academic achievement compared to control participants, and deficits in sustained attention and executive functioning that exceed the level that would be expected based on IQ (Lewandowski et al., 2007). While children with 22q11DS and the Met allele performed significantly better than their Val peers on intellectual ability and academic achievement, they were still significantly below the norm for children in the same age range on Verbal IQ, Performance IQ, Full Scale IQ, and mathematics achievement. This suggests that differences in performance on the CPT-AX, WISC, and WIAT-II between the Val and Met groups is not simply a function of poorer overall functioning, but represents differential deficits that may help partial variance within groups with 22q11DS.

Behavioral and Social Functioning and COMT Genotype

It was hypothesized that the Val group would exhibit more behavioral problems such as withdrawal, aggression, and externalizing traits, and lower overall competency based on the CBCL, as the Val allele has been associated with deficits in planning and

consequencing, behavioral disinhibition, and social withdrawal. Patients with the Val allele were rated as significantly poorer than their peers with the Met allele on the SSRS Assertion scale, and exhibited deficits in total Social Skills, as was hypothesized. Medium to large effect sizes were seen in terms of aggression, withdrawal, and externalizing problems, and overall competency, with patients with the Val allele showing more difficulties than patients with the Met allele. These findings were not statistically significant, and we are thus unable to determine whether the lack of significance is due to lack of group differences or to low power.

It should be noted that both groups were rated as being significantly impaired on overall competency, as well as on the Somatic, Social, and Attention problem scales. However, only children with the Val allele were more than one standard deviation above the mean on the Withdrawn, Anxious/Depressed, Internalizing, and Total Problem scales. This indicates that children with 22q11DS exhibit deficits compared to the general population on several indices of childhood behavioral functioning, and that, within this group, children with the Val allele have particular difficulties with behavioral and affective regulation. Thus, patients with the Val allele exhibit increased behavioral difficulties and more social problems than patients with the Met allele, and these difficulties are in domains that have been associated with children who later develop schizophrenia.

It was also predicted that the Met group would exhibit more anxiety, depression, and internalizing problems based on findings that the Met allele is associated with affective reactivity. However, patients with the Met allele actually exhibited fewer

symptoms of anxiety and depression than patients with the Val allele. Several factors may have affected this finding. First, all measures of behavioral and social functioning were based on third-party report, which requires respondents to base their answers on observable behaviors or to guess at the child's experiences. This may be especially problematic in terms of estimating internalizing difficulties, as they are more difficult to see than externalizing behaviors or social deficits. It is also possible that children with the Val allele are more behaviorally dysregulated and have poorer problem-solving and planning skills. These difficulties may reduce a child's ability to regulate affect and/or behavioral responses to difficult emotions including anger, frustration, or sadness, resulting in actual differences in anxiety and depression symptoms, or higher caregiver reports of these experiences based on observation. Alternatively, the effects of the *Val*¹⁵⁸*Met* polymorphism on affective processing may be dependent on maturational factors, such that these differences do not emerge until later adolescence or adulthood. Epidemiological studies indicate that the average age of onset of depression is during adolescence, and that rates of depression – especially in girls – increase sharply at this time (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). This is likely associated with neurological and histochemical changes that occur around the onset of puberty, many of which involve the dopamine system (Angold & Costello, 2006). Finally, it is possible that the Met allele is associated with hyperresponsivity to affective stimuli, as has been reported, but that these associations are not seen in patients with 22q11DS. Amongst the many disruptions to development and neurological functioning, it is possible that the effects of COMT genotype on affective processing are not significant in this population

over and above the effects of other genetic or biological factors. As the present sample matures, it may be beneficial to include self-report measures of anxiety and depression that can be completed by the participants themselves, and to examine changes in patterns of affective responding in order to better understand these associations.

Childhood Psychopathology and COMT Genotype

It was predicted that participants with the Val allele would exhibit deficits in global functioning compared to their peers with the Met allele. Additionally, it was predicted that the Val group would exhibit especially high rates of AD/HD, ODD, or conduct problems, which are associated with poor planning, poor working memory, or decreased behavioral inhibition. AD/HD has been associated with difficulties in sustained attention, planning and sequencing, and behavioral inhibition – tasks that it was hypothesized the Val group would exhibit deficits on compared to the Met group. Conversely, the Met allele has been associated with anxiety disorders, and symptoms involving hyperresponsivity to negative stimuli. However, there were no differences in rates of any psychopathology between groups. These findings do not appear to be due to low overall rates of psychological disorders in our young sample or underreporting by parents and caregivers of children with 22q11DS, as the rate of psychopathology was 63% in the 22q11DS group – significantly higher than the rate of psychopathology in healthy control participants (Lewandowski et al., 2007).

Note that, while the incidence of psychotic disorders appears to be significantly elevated in people with 22q11DS, psychosis was a rule-out criterion for recruitment into this study, as we are hoping to examine vulnerability to psychosis rather than correlates

of the disorder itself. Thus, comparisons between the Val and Met groups in terms of psychosis were not able to be conducted. However, longitudinal follow-up of our participants is planned, and we expect to see psychotic disorders emerge in a subset of our participants as they enter the window of risk. Examination of the relationship between the *Val*¹⁵⁸*Met* polymorphism and psychotic symptoms will be possible as our sample ages and psychotic symptoms begin to present themselves. Furthermore, symptoms of psychopathology, subclinical psychotic symptoms, behavioral characteristics and social functioning prior to the onset of frank psychosis will continue to be examined as our cohort develops, permitting the investigation of these symptom and trait features with emergent psychosis.

While it does not seem that the COMT *Val*¹⁵⁸*Met* polymorphism was associated with diagnosis of childhood psychopathology in our 22q11DS sample, children with the Val allele exhibited more social and behavioral deficits than children with the Met allele in the present sample. Thus, it may be that COMT genotype is more strongly associated with behavioral markers of underlying pathophysiology than with broad diagnostic categories in children with 22q11DS. The present findings, along with a recent report by Bearden et al. (2005), found that the Val allele was associated with greater social problems, withdrawal, and delinquency in children with 22q11DS. Such behavioral difficulties have been associated with premorbid adjustment in people who later develop schizophrenia based on retrospective reports and prospective follow-up (Bearden et al., 2000; Cannon et al., 1997; Jones et al., 1994). Thus, the COMT *Val*¹⁵⁸*Met* polymorphism may be associated with behavioral dysfunction in children similar to the dysfunction seen

in premorbid schizophrenia, indicating that behavioral and psychosocial measures of dysfunction may be more strongly associated with the polymorphism that overt psychopathology in nonpsychotic children with 22q11DS. Additionally, the mean age of the children in the present report is approximately 9.5 years. As the present sample enters adolescence, more distinct patterns of psychopathology may begin to emerge.

In terms of global functioning, it is surprising to note that there were no differences between the Val and Met groups in terms of GAF score, given the lower intellectual functioning and academic achievement scores, and increased behavioral and social deficits in children with the Val allele. It is possible that, in the context of medical and behavioral difficulties, these academic and behavioral deficits do not predict caregiver report of children's functioning within a 22q11DS sample. This may be especially likely given that, as a group, children with 22q11DS exhibited deficits in most domains assessed relative to healthy children – to whom parents may be comparing their children when asked to report on global functioning. Indeed, a previous report found that GAF scores differed between 22q11DS patients and control participants, with 22q11DS patients functioning significantly below the level of the control group (Lewandowski et al., 2007).

Haplotype Analyses

Seven of the 21 participants for whom genetic data was available were identified as haplotype-positive. Patients who were haplotype-positive exhibited deficits in a number of cognitive domains including executive functioning, behavioral inhibition, working memory, processing speed, IQ, and math achievement compared to haplotype-

negative participants. Additionally, patients who were haplotype-positive exhibited poorer assertion and lower overall behavioral competency and social skills, and greater difficulties on social and behavioral measures. These findings suggest that patients with 22q11DS and a 2-or 3-marker COMT haplotype exhibit cognitive and behavioral deficits in general, and in specific areas that have been associated with premorbid functioning in patients who develop schizophrenia.

Additionally, one participant had the 3-marker haplotype described by Shifman et al. (2002). This patient's cognitive and behavioral functioning was described, and compared to the 22q11DS group as a whole. This participant exhibited deficits in all cognitive domains compared with normative data, and deficits in sustained attention and verbal learning and memory that were at least one standard deviation from the mean of the 22q11DS group as a whole. These findings suggest that, compared with other children with 22q11DS, this patient was performing at the level that would be expected in terms of general intellectual ability and academic achievement, but exhibited specific difficulties in sustained attention and verbal learning. Unfortunately, WCST data were not available for this patient.

Additionally, this patient exhibited behavioral difficulties on the Withdrawn and Anxious/Depressed scales that were more than one standard deviation from the mean of the 22q11DS group and significantly higher than normative data. Conversely, based on the questionnaire data, this patient exhibited significantly fewer behavior problems on the attention scale than the 22q11DS group as a whole, and scored in the average range on measures of externalizing difficulties based on normative data. These findings suggest

that this patient exhibited specific difficulties in internalizing behaviors but not externalizing behaviors as compared to the general population and within a sample of patients with 22q11DS. It is important to remember that these scores represent the unique functioning of a single participant who was positive for the 3-marker haplotype, and are thus descriptive only. However, the findings suggest that the 3-marker haplotype may be associated with cognitive and behavioral difficulties that have been associated with premorbid functioning in schizophrenia, and may be involved in the neurodevelopment of psychosis. Together, these findings represent the first investigation of putative schizophrenia susceptibility haplotypes in 22q11DS specifically, and in high-risk samples generally. Findings suggest that further investigation of these haplotypes is warranted.

COMT and Markers of Schizophrenia

The present findings indicate that the COMT *Val*¹⁵⁸*Met* polymorphism is associated with cognitive and behavioral functioning that is related to premorbid adjustment in schizophrenia. This suggests that COMT may play a role in neurodevelopment of vulnerability, although findings linking COMT with increased rates of schizophrenia have been inconclusive. Rather, COMT may be more closely associated with specific neurocognitive and behavioral features than with diagnostic categories. While a number of behavioral and prefrontal cognitive measures were associated with genotype in the present study, broad measures of psychopathology were not. Additionally, within the 22q11DS group, the Val allele was associated with measures of behavioral, social, and cognitive dysfunction that have been detected in patients with

schizophrenia at premorbid, prodromal, active, and residual phases of illness. This suggests that, while COMT does not demonstrate clear linkage to schizophrenia, genotype may be associated with pathophysiological processes that contribute to vulnerability to psychosis and are detectable in behavioral and cognitive manifestations of neuromaldevelopment. Additionally, within 22q11DS, the present findings support the hypothesis that COMT genotype is associated with specific cognitive and behavioral impairment within a high-risk population. Longitudinal studies will help clarify the relationship of these specific deficits to vulnerability to psychosis.

COMT and Endophenotype Analysis

Endophenotypes are hypothesized to offer more immediate links to candidate genes than fully expressed clinical disorders. As such, this concept has utility in examining genetic inheritance, especially in complex diseases such as schizophrenia in which there may be multiple heritable dimensions (Cannon, 2005). This indicates that specific features of schizophrenia may be more directly associated with distinct genetic and pathophysiological processes, and the identification of such endophenotypes may hasten the discovery of genes and pathways of influence in the neurodevelopment of psychosis. Gottesman and Gould (2003) delineated several key criteria for endophenotypes, including an association with a specific gene or gene region, association with the disease, and heritability as detected in relatives. The present findings support the examination of cognitive, and possibly behavioral and social, dysfunction as endophenotypes in schizophrenia, in keeping with the description by Gottesman and Gould. Specific cognitive and behavioral deficits were detected in the present sample of

patients with 22q11DS, and were associated with the COMT *Val*¹⁵⁸*Met* polymorphism. As described above, these cognitive and behavioral deficits have been associated with patients with schizophrenia at all phases of illness, and in other high-risk populations including first-degree relatives. Additionally, the COMT *Val*¹⁵⁸*Met* polymorphism may be more strongly associated with these cognitive and behavioral features than has schizophrenia itself. Thus, the present findings support previous suggestions that cognitive (and possibly behavioral) deficits may represent endophenotypes in schizophrenia (Cannon, 2005). Associations of COMT with putative endophenotypes in schizophrenia may yield tighter correlations than examination of COMT with diagnostic category, and may provide important information about disruptions in neurodevelopment and neurobiology that are associated with psychosis. Better understanding of these relationships holds the promise of elucidating etiological and pathophysiological pathways in the development of the disease, and may hasten the development of treatments specifically targeted at these substrates.

It is likely that “intermediate phenotypes” including brain activity in regions of interest more sensitively measure gene effects (Smolka et al., 2005). Indeed, examinations of brain functioning found that efficiency of processing in prefrontal cortex based on fMRI, and in the cingulate cortex on a task of attentional control, was significantly better in *Met* subjects (Egan et al., 2001; Heinz & Smolka, 2006). Genotype was associated with activation of frontal and limbic regions during presentation of aversive emotional stimuli, but was unrelated to measures of anxiety or depression (Heinz & Smolka, 2006; Smolka et al., 2005). Egan et al. (2001) found that *Val* allele

load predicted less efficient prefrontal response on the WCST in patients with schizophrenia, their unaffected siblings, and healthy controls. Similarly, McIntosh et al. (2007) found that the Val allele was associated with increased activation in lateral prefrontal cortex and anterior and posterior cingulate as task demands increased despite a similar level of performance on the tasks. Less direct measures of outcome may be affected by brain activity that reflects compensatory strategies and/or effects of genetic variation not associated with COMT, which may dilute findings. The more directly specific aspects of brain functioning are measured, the stronger the association between genotype and outcome. Functional imaging of prefrontal regions in association with the COMT genotype in patients with 22q11DS may continue to elucidate these relationships. Additionally, this suggests that the specificity of measures to hypothesized constructs of interest should be carefully considered in study design.

Neurodevelopment, Cognitive Functioning, and COMT

Based on the hypothesis that schizophrenia is an extreme manifestation of a process of neuromaldevelopment, it is assumed that, for patients with the vulnerability, the brain is already developing along a disrupted trajectory, which likely involves the prefrontal cortex (PFC). Indeed, we see poor prefrontal functioning in our 22q11DS patients as a whole relative to normal controls and over and above the level that would be expected based on intellectual abilities (Lewandowski et al., 2007). Additionally, patients with the Val allele perform especially poorly on several measures of working memory, reasoning, and attention.

Based on a developmental model, we would expect to see attenuated deficits on specific tasks until the brain region presumed to mediate performance on such tasks is fully-developed. Thus, the timing of development in PFC is an important variable in the investigation of schizophrenic-like deficits in patients with 22q11DS. This is because typically-developing children would be expected to improve substantially on tasks that recruit the PFC as this region matures; however, it is hypothesized that children with disruptions in PFC will exhibit increasing deficits relative to their peers as neurodevelopmental processes act on already disrupted pathways.

In primates, functional maturation of the PFC is protracted, with adult levels of functioning not being reached until puberty (Chugani & Chugani, 1997). Frontal lobe activity is enhanced on tasks requiring higher-level processing during adolescence and young adulthood, despite a reduction in total volume and metabolism in PFC during adolescence (Casey, Geidd, & Thomas, 2000; Rubia et al., 2000). Gray matter volume reductions in cortical areas reflect planned pruning and refinement of connections, and are related to enhanced performance on tasks that are mediated by this region (Giedd et al., 1999; Jernigan, Trauner, Hesselink, & Tallal, 1991; Sowell & Jernigan, 1998; Sowell, Thompson, Tessner, & Toga, 2001). This suggests that volumetric decreases in cortical areas during adolescence reflect refinement rather than degeneration.

Neurodevelopment in adolescence. In adolescence, the peak of brain activity occurs in PFC. Evidence from tasks believed to tap functioning in this region indicates that many of these are too difficult for young children but become much more manageable for adolescents as brain development in the PFC reaches maturity.

Maturational processes allow for refinements of existing abilities including speed and capacity of information processing (Luna & Sweeny, 2004). A study of healthy 9-18 year-olds found significant age-effects in abstract reasoning, response inhibition, and attentional set shifting, with these skills becoming available during peripuberty and continuing to improve throughout adolescence (Rosso, Young, Femia, & Yurgelun-Todd, 2004). Thus, functioning that is dependent on PFC should be severely impaired by anomalies involving in development during and after adolescence, but should be less affected in early years when brain metabolic activity is lower in frontal areas (Vicente & Kennedy, 1997)

Indeed, while cognitive and behavioral deficits are often present throughout childhood in people who will go on to develop schizophrenia, cognitive deficits and academic and behavioral problems increase in adolescence (Fuller et al., 2002), supporting a role of PFC dysmaturation in schizophrenia. It is presumed that typical neurodevelopmental processes further compromise structure and function of PFC leading to increased deficits in functioning with regard to tasks mediated by this region. Furthermore, increased relative impairments in preschizophrenic adolescents may be reflective of increasing task demands surrounding social and cognitive performance mediated by PFC. Thus, these demands are easier to meet for typically-developing adolescents than for preschizophrenic adolescents, whose PFC structure and connectivity are compromised.

There is evidence of over-pruning in dorsolateral PFC in schizophrenic patients, in which normal pruning processes are exceeded (Giedd et al., 1999; Selemon,

Rajkowska, & Goldman-Rakic, 1995). This may result from an excess of unused connections due to errors in neuronal migration and organization, or reduction of opportunities for long-term potentiation, suggesting that neural abnormalities in PFC that occurred during brain development and organization and were resultantly unusable during childhood become subject to over-pruning in adolescence. Additionally, imaging studies have suggested that the PFC may be reduced in size and functioning in schizophrenic patients compared to controls (Berman, Torrey, Daniel, & Weinberger, 1992; Black et al., 2004; Glantz & Lewis, 2000; Gur et al., 2000; Selemon, Rajkowska, & Goldman-Rakic, 1995). A large body of evidence suggests that people with schizophrenia experience diminished PFC functioning, or hypofrontality, during working memory tasks, as well as logical reasoning and other tasks that are mediated by this region (Barch et al., 2001; Callicott et al., 2000; Carter et al., 1998; Fletcher et al., 1998; Ramsey et al., 2002; Stevens et al., 1998). Weinberger, Berman, and Illowski (1988) found that patients with schizophrenia showed reductions in regional cerebral blood flow (rCBF) in dorsolateral PFC during the WCST, but not during number-matching task, which is a non-prefrontal measure. Additionally, patients with schizophrenia did not activate dorsolateral PFC above their baseline (based on the number-matching task) during the WCST performance.

The average age at assessment of the present sample was approximately 9 years. Thus, we would expect that performance on tasks that require PFC activation in this group of patients with 22q11DS to worsen compared to their healthy peers as the prefrontal cortex reaches maturity. Since this does not happen until adolescence or early

adulthood, we would expect that relative deficits in functioning will continue to increase as our sample reaches young adulthood.

Additionally, it is possible that the mechanisms within the prefrontal cortex that affect functioning in this region may play a more apparent role as development progresses. In the present sample, the COMT *Val*¹⁵⁸*Met* polymorphism, which has a substantial effect on prefrontal dopamine levels, may become more strongly associated with performance on tasks that assess functioning mediated by this region. Conversely, the relationship between the *Val*¹⁵⁸*Met* polymorphism and prefrontally-mediated functioning may change in more complex ways. For instance, cognitive tasks assessed in the present study are presumed to be affected by prefrontal dopamine functioning. The present findings suggest that, consistent with findings from other samples with 22q11DS as well as nondeleted participants, patients with the Val allele perform worse on such tasks due, at least in part, to reductions in dopamine availability. However, as Weinberger noted, there is likely an “optimal” window of dopamine availability in PFC, such that reductions in dopamine (as seen in Val/Val individuals) and excesses in dopamine may result in similar detriment to performance on tasks that rely on this process. As a result, development may interact with dopamine functioning in 22q11DS such that dopamine changes in adolescence move patients with the Met allele out of the optimal window of dopamine availability, resulting in poorer cognitive functioning in young adulthood. Again, longitudinal investigation of the present sample will help elucidate some of these questions.

In sum, deficits in prefrontally-mediated functioning are evident in patients with 22q11DS in childhood – well before maturation in this region is completed and well before expected onset of symptoms. This is consistent with a neurodevelopmental model of schizophrenia, and suggests that cognitive and behavioral impairments will worsen as our sample reaches adolescence and early adulthood. COMT may play a role in disrupted functioning in this region, as it affects dopamine regulation in the synapse. Additionally, COMT may play a role in neurodevelopment and pathophysiology of schizophrenia, affecting dopaminergic functioning in prefrontal regions in particular, which have been hypothesized to play a central role in the etiology and pathogenesis of psychosis. In addition to dysfunction on prefrontally-mediated cognitive tasks, it would be expected that COMT would be associated with other social and behavioral deficits that are likely affected by prefrontal functioning. Indeed, the present findings suggest that social and behavioral impairments are associated with COMT genotype. Developmentally, this may set the stage for continued disruption in development through childhood and into adolescence and early adulthood, as discussed above.

Gene-By-Gene Interactions and Haplotype Analysis

It is likely that complex interactions affect the relationship of COMT on phenotypic outcome measures in schizotypy, including diagnosis. The *Val¹⁵⁸Met* polymorphism may interact with other loci in the COMT gene and with other genes. Indeed, preliminary examination of COMT haplotypes described by Shifman et al. (2002) and Funke et al. (2005) in the present sample of patients with 22q11DS suggest that these haplotypes are more common in patients with 22q11DS than in a previously identified

control group, and are associated with schizophrenic-like cognitive and behavioral deficits. Additionally, the *Val*¹⁵⁸*Met* allele may interact with genes in other regions, creating complex gene-by-gene interaction effects. For instance, Nicodemus et al. (2007) reported a significant increase in risk for schizophrenia associated with three RGS4 SNPs in interaction with COMT, while the main effects for RGS4 SNPs were null. In healthy subjects, Smolka et al. (2007) observed an additive effect of the COMT Met and 5-HTT low expressing alleles on regional blood oxygen level-dependent response to aversive stimuli, with the interaction accounting for 40% of the inter-individual variance. Haplotype and gene-by-gene analyses such as these may improve prediction not only in terms of schizophrenia, but in terms of cognitive and behavioral features associated with psychosis. These findings, together with preliminary data from the present investigation, support the extension of haplotype analyses to more homogeneous features associated with schizophrenia, including putative endophenotypes. While these studies require large samples, as the likelihood of achieving a group of sufficient size to detect differences decreases exponentially with each marker that is added to the haplotype, they may yield more robust associations between genotype and phenotype.

Finally, it is important to remember that the *Val*¹⁵⁸*Met* polymorphism is in Hardy-Weinberg equilibrium, meaning that it is distributed throughout the population. This suggests that, while COMT may play a role in etiology and pathogenesis of psychosis, it is unlikely that this gene is causally related to schizophrenia in a monogenic fashion. It is more likely that COMT is associated with an endophenotype of schizophrenia, and plays

a role in the complex neurodevelopment of psychosis, along with many other genes and interactions.

COMT Interactions by Sex, Environment, and Maturation

In addition to gene-by-gene interactions, other factors likely interact with COMT to affect phenotypic expression. Such factors may include environmental effects on brain and gene expression and the effects of maturational processes and sex on outcome measures. For instance, the COMT Met allele was associated with anxiety in women but not in men (Enoch et al., 2003), and a recent report found that COMT genotype predicted general intelligence in boys but not girls, and that these effects increased with maturation (Barnett et al., 2007). In fact, one would expect these differences to become much more pronounced with the onset of puberty. This suggests that sex and maturational factors can moderate the effects of COMT genotype on phenotype. While our sample size was not sufficient to examine effects by sex, the groups did not differ on the proportion of males and females. As the sample increases, these analyses will be important to consider. Additionally, as our sample continues to age, the effects of maturational variables in combination with gender will be increasingly important.

Exposure to environmental factors that play a role in schizophrenia pathogenesis may also interact with genotype in complex ways. Caspi et al. (2005) reported that psychotic symptoms and diagnosis of schizophreniform disorder were not associated with COMT genotype. However, they found a significant interaction between genotype and adolescent cannabis use in people who reported psychotic symptoms or met criteria for schizophreniform disorder. Interestingly, there was no interaction effect of adult onset

cannabis use and genotype on diagnosis of schizophreniform disorder or reported psychotic symptoms, suggesting that this interaction may be sensitive to maturational variables. These findings indicate that gene associations may remain undetectable absent environmental risk, reducing the likelihood of detection of reliable associations (Caspi et al., 2005). Similar gene-by-environment findings – absent main effects of the genetic marker – have been detected in other studies of complex human disease (Caspi et al., 2002; Caspi, Sugden, Moffitt, Taylor, & Craig, 2003; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005). Such complex analyses require large samples and longitudinal follow-up, and will be important to consider as we follow our participants over time.

Additionally, effects of maturation and timing of exposure may be of importance, and maturational factors may be important in terms of measurement, as well. For instance, given the apparent role of COMT in prefrontal functioning and the protracted nature of maturation in this brain region, with adult-level structural, functional, and cognitive outcomes not reached until late adolescence or early adulthood, effects of compromised neurotransmitter regulation in this region may not be apparent until adult levels of prefrontally-mediated functioning are achieved, as discussed above. Similarly, exposure to risk factors believed to affect prefrontal pathways may have no detectable effect on phenotype if the exposure occurs outside of a developmentally-sensitive period. This underscores the importance of theoretically-driven hypothesis testing, as such models can attempt to account for maturational factors *a priori*. Within our present sample, a number of factors should be examined in terms of insults to maturation and neurodevelopment as our sample size permits. For instance, there is considerable

heterogeneity in our sample in terms of medical complications and interventions, including perinatal complications, exposure to general anesthesia, time spent in the hospital, immunological deficiencies, and cardiac and palate abnormalities. Additionally, factors like parental psychopathology, especially schizotypy and schizophrenia, should be considered, as there may biological and environmental effects on children based on having a parent with psychosis. These factors and their timing may affect neural development, and should be accounted for as our sample increases in size enough to group patients based on these factors, and through longitudinal follow-up to examine the effects on functioning through development.

While evidence for a causal role in schizophrenia remains inconclusive, COMT continues to represent a promising candidate for examination of genetic effects on the pathogenesis of schizophrenia and related disorders. However, associations between genotype and specific symptoms and markers – rather than the “syndrome” of schizophrenia itself – may hold more promise. In fact, issues with associations between biological markers and heterogeneous disorders such as schizophrenia have been noted for decades. Luchins (1975) suggested, “...that research directed towards studying dopaminergic mechanisms in specific psychopathological symptoms, not syndromes, might prove fruitful.” Thus, associations between COMT and endophenotypes should be pursued. Such investigations provide logical starting points, as complex disorders are characterized by a variety of disparate symptoms, and classification strategies often produce groups that are not homogeneous. Additionally, it is simultaneously unlikely that a single gene or SNP will account for substantial variance in complex human disease

and likely that a single gene or SNP will be associated with multiple outcomes. This may account for both failures to replicate associations, and non-specific associations between a genetic locus and multiple variables. Investigations of gene associations should be driven theoretically by hypothesized or known effects on functioning, and these outcome measures may be linked to the neurodevelopment of vulnerability to schizophrenia, movement along the continuum, decompensation, or protective factors.

Other factors may reduce the strength of the association between COMT functioning and schizophrenia, including compensatory brain functioning and other protective factors, and the heterogeneity of schizophrenia itself as it is currently formulated. For example, schizophrenia and schizotypy have been hypothesized to be multidimensional constructs, with candidate factors including positive, negative, and cognitive disorganization (e.g. Claridge et al., 1996; Lewandowski et al., 2006; Mason, Claridge, & Williams, 1997; Vollema and van den Bosch, 1995). Disease course, associated traits, and treatment efficacy associated with these factors may actually be distinct. Positive schizotypy has been associated with higher rates of depression and anxiety symptoms (Lewandowski et al., 2006), and negative schizotypy has been associated with social disinterest (Brown et al., in press). Negative (but not positive) symptoms are correlated with greater impairment in cognition and social functioning (McGurk et al., 2000), and negative symptoms are more persistent, while positive symptoms tend to decrease with age (Fenton & McGlashan, 1991). Cognitive impairment is associated with poor community functioning (Green, Kern, & Heaton, 2004), and may be a stronger correlate of poor outcome than any other symptom domain

(Green, 1996). Additionally, pharmacological therapies tend to address positive symptoms more effectively than negative symptoms and cognitive disorganization, although atypical antipsychotics appear to confer some improvement in these domains compared with their older-generation counterparts (Burton, 2006). Examination of biological variables in association with schizotypy factors may help increase the likelihood of finding meaningful associations between grouping variables and genetic or neurobiological factors that may be washed out in more heterogeneous groups (Lewandowski, in press). Thus, caution must be exercised when describing associations between COMT and schizophrenia, and strategies that attempt to link COMT (or any other genetic) variation to specific symptoms may prove more fruitful.

Future Directions

The present study is a cross-sectional examination of the association of COMT genotype and cognitive and behavioral risk markers of psychosis in a putatively schizotypic sample. These findings represent preliminary data regarding these associations, as well as preliminary descriptions of a COMT haplotype in 22q11DS. Interpretations of the present findings were limited by sample size, which underpowered the study. Additionally, the small sample size prevented the investigation of the possible effects of variables such as age and gender on outcome measures. As the sample size increases, such investigations will be permitted, which may demonstrate the presence of complex interactions amongst variables. Additionally, the present sample is being followed prospectively. As follow-up data become available, the relationships of genetic, cognitive, and behavioral variables with the development of psychopathology, and

schizophrenia-spectrum disorders specifically, can be examined. Prospective investigation will inform the utility of cognitive and behavioral deficits as endophenotypes, as has been hypothesized. Specifically, cognitive processes that involve frontal lobe-mediated working memory and executive functioning may represent a distinct heritable dimension in schizophrenia (Cannon, 2005).

Children with 22q11DS exhibit an array of cognitive, behavioral, and psychiatric difficulties that may have implications for later psychiatric outcome and adjustment. Identification of features that precede the onset of clinical symptoms is important in understanding the neurodevelopmental processes that contribute to later adjustment, as well as the development of early intervention strategies (Murphy, 2005). Substantial heterogeneity of symptoms exists among individuals with this syndrome. Continued examination of cognitive and behavioral deficits within this group may help confirm specific risk markers for the development of psychosis. Continued investigation of this population, including studies of premorbid and prodromal symptoms and areas of dysfunction, may help refine our understanding of which children will go on to develop schizophrenia. Additionally, such work may improve our understanding of the etiological pathway(s) of schizophrenia and clarify factors that further contribute to risk. Such an understanding may increase accuracy in identification of persons at risk, improving the effectiveness of prophylactic treatment efforts.

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APPENDIX A. TABLES

Table 1

Group Demographic Characteristics

	Met	Val
	(<i>n</i> = 13)	(<i>n</i> = 14)
Age	9.1 (2.0)	9.7 (3.1)
Gender	38% female	36% female
Ethnicity	100% Caucasian/ 0% African American	86% Caucasian/ 14% African American
Social Position	37.7 (12.5)	36.1 (15.8)
Education (years)	1.9 (1.7)	2.6 (3.0)
Global Adjustment	63.9 (9.5)	59.1 (10.0)

Note: all comparisons were non-significant

Table 2

Means and Standard Deviations of Neurocognitive Measures by Group

	Met (n=13)	Val (n=14)	<i>t</i> -test	Cohen's <i>d</i>
Continuous Performance Test				
CPT-IP	.14 (.26)	.31 (.33)	-1.52	-.57
AX	1.42 (.77)	.88 (1.02)	1.55 [†]	.60
Wisconsin Card Sorting Test				
Perseverative	86.2 (10.0)	89.8 (11.6)	-.85	-.33
Non-Perseverative	86.5 (11.3)	80.8 (21.2)	.86 [†]	.34
% Conceptual Level	85.1 (8.2)	80.8 (15.6)	.88	.35
California Verbal Learning Test-Children's Version				
List A1-5z	-1.07 (.74)	-1.09 (1.18)	.04	.02
List A1	-.77 (1.38)	-.71 (1.44)	-.10	-.04
Short Delay Free	-.77 (.73)	-1.00 (1.41)	.53	.20
Short Delay Cued	-.96 (.75)	-1.39 (1.39)	.99	.39
Long Delay Free	-1.12 (1.12)	-1.25 (1.53)	.26	.10
Long Delay Cued	-.85 (1.13)	-1.25 (1.41)	.82	.31
Serial Clustering	-.54 (.80)	-.50 (1.00)	-.11	-.04
Semantic Clustering	.00 (.91)	-.04 (1.29)	.08	.04

[†] : Equality of Variances not met (Levene's Test, $p < .05$), so *t* statistics reported and corresponding *p* values are based on unequal variances.

Table 3

WISC-III Means and Standard Deviations by Group

	Met (<i>n</i> = 13)	Val (<i>n</i> = 14)	<i>t</i> -test	Cohen's <i>d</i>
<i>Scale Scores</i>				
Full Scale IQ	76.1 (10.7)	66.1 (12.4)	2.19**	.86
Verbal IQ	79.6 (10.0)	70.0 (12.1)	2.18**	.86
Performance IQ	76.5 (11.4)	70.2 (14.2)	1.25	.49
<i>Factor Scores</i>				
Verbal Comprehension	80.6 (10.1)	72.0 (13.0)	1.83*	.74
Perceptual Organization	76.7 (11.8)	68.5 (14.4)	1.60	.62
Working Memory	83.3 (12.0)	70.1 (14.2)	2.40**	1.00
Processing Speed	86.0 (16.0)	73.3 (13.8)	2.09**	.85
<i>Subtest Scores</i>				
Block Design	6.0 (3.1)	4.7 (2.7)	1.16	.45
Similarities	6.9 (2.6)	5.4 (2.9)	1.35	.54
Digit Span	7.2 (2.4)	5.8 (2.7)	1.27	.55
Coding	6.9 (2.7)	5.8 (3.1)	1.02	.38
Vocabulary	6.1 (2.3)	4.8 (2.5)	1.34	.54
Comprehension	5.8 (2.9)	4.5 (3.3)	1.02	.42
Symbol Search	7.5 (3.8)	4.3 (2.7)	2.36**	.97
Information	6.7 (2.6)	5.0 (1.7)	1.68	.77
Arithmetic	6.0 (2.4)	3.4 (3.5)	1.98*	.87

Picture Completion	5.9 (2.9)	3.8 (1.7)	1.94*	.88
Picture Arrangement	6.1 (2.4)	2.8 (1.6)	3.56***	1.62
Object Assembly	5.3 (2.7)	4.8 (3.6)	0.40	.16

*** = $p < .01$

** = $p < .05$

* = $p < .10$

Table 4

WIAT-II Means and Standard Deviations by Group

	Met (<i>n</i> = 13)	Val (<i>n</i> = 14)	<i>t</i> -test	Cohen's <i>d</i>
Broad Reading	87.8 (16.4)	76.4 (19.1)	1.62	.64
Word Reading	88.8 (9.9)	77.9 (20.0)	1.68	.69
Reading Comprehension	84.6 (17.0)	73.8 (19.5)	1.47	.59
Pseudoword Decoding	94.1 (17.0)	85.7 (17.5)	1.06	.49
Broad Mathematics	77.3 (14.2)	65.5 (16.9)	1.96*	.76
Math Reasoning	82.2 (15.3)	66.4 (14.3)	2.78**	1.07
Numerical Operations	78.1 (12.6)	69.6 (19.8)	1.31	.51
Spelling	85.9 (13.3)	76.8 (19.3)	1.42	.55

*** = $p < .01$ ** = $p < .05$ * = $p < .10$

Table 5

CBCL Means and Standard Deviations by Group

	Met (<i>n</i> = 13)	Val (<i>n</i> = 14)	<i>t</i> -test	Cohen's <i>d</i>
Competency Total	36.0 (9.0)	32.5 (4.1)	1.07	.50
Problem Scales [†]				
Withdrawn	58.5 (6.3)	62.9 (8.6)	-1.3	-.58
Somatic	64.4 (8.8)	63.5 (11.3)	.20	.09
Anxious/Depressed	55.9 (6.8)	63.1 (8.2)	-2.14**	-.96
Social	62.3 (12.3)	64.1 (7.7)	-.39	-.18
Thought Problems	59.7 (10.9)	58.6 (10.0)	.24	-.18
Attention	64.8 (9.2)	62.7 (10.5)	.48	.21
Delinquent	55.2 (5.6)	54.8 (6.1)	.15	.07
Aggressive	52.9 (3.7)	57.5 (6.1)	-2.03*	-.91
Internalizing	54.2 (17.8)	62.8 (14.7)	-1.12	-.53
Externalizing	50.0 (8.2)	54.9 (9.4)	-1.24	-.56
Total Problem	59.2 (10.2)	62.4 (11.4)	-.66	-.30

[†] Note: Higher scores on problem scales indicate poorer functioning.

** = $p < .05$ * = $p < .10$

Table 6

SSRS Means and Standard Deviations by Group

	Met (<i>n</i> = 13)	Val (<i>n</i> = 14)	<i>t</i> -test	Cohen's <i>d</i>
Social Skills Scale				
Cooperation	10.8 (2.7)	9.7 (4.1)	.75	.32
Assertion	16.7 (2.8)	11.9 (3.9)	3.23***	1.41
Responsibility	13.6 (3.5)	11.0 (5.0)	1.38	.60
Self-Control	11.6 (2.3)	11.2 (4.6)	.27	.11
Skills Total (Standardized)	98.8 (13.9)	84.9 (21.7)	1.74*	.76
Problem Scales[†]				
Externalizing	3.5 (1.7)	4.5 (2.7)	-1.01	-.44
Internalizing	4.8 (2.0)	5.6 (3.0)	-.71	-.31
Hyperactivity	5.2 (3.0)	6.4 (4.7)	-.64	-.30
Problem Total (Standardized)	104.1 (14.0)	108.3 (16.4)	-.64	-.28

[†] Note: Higher scores on problem scales indicate poorer functioning.

*** = $p < .01$ * = $p < .10$

Table 7

Childhood Psychopathology and Global Functioning by Group

	Met (<i>n</i> = 13)	Val (<i>n</i> = 14)	Fisher's Exact Test
Social Phobia	0	2	.48
Separation Anxiety	2	1	.60
Specific Phobia	5	4	.70
Panic Disorder	1	0	.48
Agoraphobia	1	0	.48
Generalized Anxiety	2	0	.22
OCD	2	2	1.00
PTSD	0	1	1.00
Any Anxiety Dx	5	8	.45
Major Depression	1	0	.48
Depression NOS	0	1	1.00
Any Depressive Dx	1	1	1.00
AD/HD	7	4	.25
Oppositional-Defiant	2	4	.65
Any Diagnosis	7	10	.44
	Met (<i>n</i> = 13)	Val (<i>n</i> = 14)	<i>t</i> -test
Hyperactive (symptoms)	2.9	2.2	.54
Inattention (symptoms)	5.5	3.8	.16

Note: The categories Dysthymia, Bipolar I, Bipolar II, Schizophrenia, Schizoaffective, Psychosis NOS, and Conduct Disorder were not computed because there were no participants who met criteria for these diagnoses.

Table 8

Means and Standard Deviations of Neurocognitive Measures by Haplotype

	Positive (n = 7)	Negative (n = 21)	t-test	Cohen's d
Continuous Performance Test				
CPT-IP	.33 (.44)	.14 (.24)	1.27	.54
AX	.66 (1.06)	1.12 (.91)	-1.03	-.47
Wisconsin Card Sorting Test				
Perseverative	88.8 (10.4)	87.6 (11.6)	.20	.11
Non-Perseverative	67.6 (11.2)	91.2 (15.1)	-3.18***	-1.78
% Conceptual Level	71.8 (5.5)	88.1 (11.7)	-2.95***	-1.78
California Verbal Learning Test-Children's Version				
List A1-5z	-1.46 (1.07)	-.98 (1.45)	-1.27	-.38
List A1	-1.14 (1.28)	-.93 (1.45)	-.33	-.15
Short Delay Free	-1.57 (1.62)	-.75 (.80)	-1.58	-.64
Short Delay Cued	-1.50 (1.76)	-1.11 (.84)	-.70	-.28
Long Delay Free	-1.43 (1.67)	-1.21 (1.17)	-.34	-.15
Long Delay Cued	-1.64 (1.70)	-.86 (1.12)	-1.28	-.54
Serial Clustering	-.43 (1.13)	-.61 (.86)	.40	.18
Semantic Clustering	.07 (.98)	.04 (1.34)	.06	.03

*** = $p < .01$

Table 9

WISC-III and WIAT-II Means and Standard Deviations by Haplotype

	Positive (<i>n</i> = 7)	Negative (<i>n</i> = 21)	<i>t</i> -test	Cohen's <i>d</i>
<i>WISC Scale Scores</i>				
Full Scale IQ	61.7 (10.4)	72.9 (12.4)	-2.03*	-.98
Verbal IQ	66.7 (10.3)	77.1 (12.3)	-1.89*	-.92
Performance IQ	64.6 (11.4)	73.7 (12.8)	-1.60	-.75
<i>WISC Factor Scores</i>				
Verbal Comprehension	68.7 (11.5)	78.5 (12.8)	-1.60	-.81
Perceptual Organization	61.5 (8.3)	72.9 (13.5)	-1.90*	-1.02
Working Memory	65.0 (9.7)	79.9 (13.0)	-2.45**	-1.30
Processing Speed	67.7 (11.3)	85.5 (16.9)	-2.32**	-1.24
<i>WISC Subtest Scores</i>				
Block Design	4.3 (2.6)	5.4 (3.2)	-.78	-.38
Similarities	5.1 (3.2)	6.8 (3.1)	-1.09	-.54
Digit Span	4.8 (2.0)	7.1 (2.3)	-2.01*	-1.07
Coding	4.6 (2.7)	7.2 (2.9)	-2.00*	-.93
Vocabulary	3.6 (1.9)	6.1 (2.5)	-2.28**	-1.16
Comprehension	3.7 (2.5)	5.2 (3.4)	-1.04	-.50
Symbol Search	3.0 (1.9)	7.1 (3.7)	-2.53**	-1.39
Information	5.0 (2.1)	6.2 (2.5)	-1.04	-.52
Arithmetic	3.0 (1.9)	5.8 (2.9)	-1.90*	-1.14

Picture Completion	3.5 (1.6)	5.6 (2.9)	-1.62*	-.90
Picture Arrangement	3.0 (1.9)	5.3 (2.8)	-1.84*	-.96
Object Assembly	5.2 (3.5)	4.9 (3.1)	0.15	.09
WIAT-II Broad Reading	77.9 (22.6)	86.6 (16.2)	-1.01	-.44
Word Reading	78.7 (23.2)	88.6 (9.9)	-1.31	-.56
Reading Comprehension	75.1 (21.7)	83.6 (17.7)	-0.92	-.43
Pseudoword Decoding	84.3 (27.5)	94.9 (16.6)	-0.84	-.47
WIAT-II Broad Math	62.9 (14.0)	74.6 (14.6)	-1.77*	-.82
Numerical Operations	63.3 (16.2)	77.1 (12.4)	-2.17**	-.96
Math Reasoning	66.0 (14.2)	78.6 (16.2)	-1.74*	-.83
WIAT-II Spelling	78.8 (21.4)	84.7 (13.5)	-0.77	-.33

*** = $p < .01$

** = $p < .05$

* = $p < .10$

Table 10

CBCL Means and Standard Deviations by Haplotype

	Positive (<i>n</i> = 6)	Negative (<i>n</i> = 21)	<i>t</i> -test	Cohen's <i>d</i>
Competency Total	33.8 (3.5)	42.0 (11.6)	-2.79**	-.96
Problem Scales [†]				
Withdrawn	62.0 (9.7)	57.0 (7.4)	1.36	.58
Somatic	62.8 (14.0)	59.2 (9.6)	.74	.30
Anxious/Depressed	61.3 (9.8)	55.5 (7.1)	1.64	.68
Social	60.3 (6.9)	59.1 (11.0)	.25	.13
Thought Problems	58.2 (10.4)	55.3 (8.7)	.68	.30
Attention	58.0 (5.4)	61.4 (11.2)	-.71	-.39
Delinquent	53.0 (5.9)	54.1 (4.4)	-.48	-.21
Aggressive	55.8 (6.1)	54.0 (5.2)	.73	.32
Internalizing	59.2 (18.2)	52.5 (15.1)	.91	.40
Externalizing	51.8 (10.3)	49.9 (9.2)	.44	.19
Total Problem	58.8 (12.6)	54.6 (12.7)	-.66	.33

[†] Note: Higher scores on problem scales indicate poorer functioning.

** = $p < .05$

Table 11

SSRS Means and Standard Deviations by Haplotype

	Positive (<i>n</i> = 7)	Negative (<i>n</i> = 21)	<i>t</i> -test	Cohen's <i>d</i>
Social Skills Scale				
Cooperation	10.0 (4.7)	11.1 (2.7)	-.76	-.29
Assertion	11.4 (3.8)	16.1 (3.6)	-2.97***	-1.27
Responsibility	11.7 (6.3)	13.4 (3.8)	-.85	-.33
Self-Control	11.3 (5.1)	12.1 (4.0)	-.46	-.17
Skills Total (Standardized)	86.1 (23.1)	98.6 (19.9)	-1.38	-.58
Problem Scales[†]				
Externalizing	3.3 (1.8)	4.1 (2.7)	-.78	-.35
Internalizing	5.0 (2.9)	4.4 (2.5)	.50	.22
Hyperactivity	5.6 (6.1)	5.2 (2.8)	.21	.08
Problem Total (Standardized)	102.3 (12.4)	104.2 (17.3)	-.28	-.13

[†] Note: Higher scores on problem scales indicate poorer functioning.

*** = $p < .01$ ** = $p < .05$ * = $p < .10$

Table 12

Cognitive Functioning in Patient with 3-Marker Haplotype

	Patient with 3-marker Haplotype	22q11DS Group
WISC-III		
FSIQ	71	71.4 (11.9)
VIQ	73	73.9 (12.1)
PIQ	73	74.3 (13.2)
WIAT-II		
Broad Reading	80	82.7 (17.3)
Reading Comprehension	63	80.6 (18.4)
Broad Mathematics	64	72.0 (16.0)
Numerical Operations	62	74.6 (17.1)
Math Reasoning	66	74.9 (15.6)
Spelling	75	82.3 (16.1)
CPT		
IP	-.17	.20 (.29)*
AX	.44	1.04 (1.03)
CVLT-C		
List A1-5z	-2.7	-1.0 (0.9)*
List A1	-2.0	-0.7 (1.3)*
Short Delay Free	-2.5	-0.8 (1.1)*
Short Delay Cued	-2.5	-1.0 (1.1)*

Long Delay Free	-2.0	-1.0 (1.3)
Long Delay Cued	-2.5	-0.9 (1.2)*
Serial Clustering	-1.5	-0.4 (0.9)*
Semantic Clustering	0.5	0.0 (1.1)

* = ≥ 1 standard deviation below the 22q11DS mean

Table 13

Behavioral and Social Measures in Patient with 3-Marker Haplotype

	Patient with 3-Marker Haplotype	22q11DS Group
CBCL Competency Total	34	34.9 (7.6)
CBCL Problem Scales [†]		
Withdrawn	73	61.2 (8.3)*
Somatic	67	62.2 (9.9)
Anxious/Depressed	69	59.4 (8.4)*
Social	65	61.8 (9.5)
Thought Problems	64	58.0 (9.6)
Attention	52	63.0 (9.9)^
Delinquent	50	54.4 (5.3)
Aggressive	52	54.7 (5.3)
Internalizing	72	58.1 (16.1)
Externalizing	48	51.6 (9.0)
Total Problem	63	59.7 (10.8)
SSRS Social Skills Scale		
Cooperation	7	10.3 (3.8)
Assertion	11	15.1 (6.7)
Responsibility	12	15.6 (18.8)
Self-Control	10	11.1 (4.1)

Skills Total (Standardized)	81	88.0 (25.6)
SSRS Problem Scales [†]		
Externalizing	4	4.2 (2.2)
Internalizing	6	5.3 (2.7)
Hyperactivity	1	9.1 (17.2)
Problem Total (Standardized)	94	106.0 (15.1)

[†] Note: Higher scores on problem scales indicate poorer functioning

* = ≥ 1 standard deviation from the 22q11DS mean

^ = ≤ 1 standard deviation from the 22q11DS mean