KACZOROWSKI, JESSICA A., Ph.D. The Impact of Catechol-O-Methyl Transferase on Working Memory in Psychometrically Identified Schizotypy. (2012)
Directed by Dr. Thomas R. Kwapil. 88 pp.

Patients with schizophrenia often exhibit impairment in working memory that is influenced by dopamine availability in the prefrontal cortex. Dopamine availability in the prefrontal cortex is regulated in part by the activity of the Catechol-O-Methyl transferase (COMT) gene. The COMT gene contains a functional polymorphism that results in a Valine (Val) to Methionine (Met) amino acid substitution that impacts dopamine availability. COMT impacts working memory performance in patients with schizophrenia such that Val allele load is associated with impaired working memory performance. The present study extended this literature by examining the relationship between COMT and spatial working memory (SWM), and their interactions, in psychometrically identified positive and negative schizotypy in a nonclinically ascertained sample of young adults. As hypothesized, negative schizotypy was associated with the Val allele in an allele dependent fashion. In addition, negative, but not positive, schizotypy was generally associated with deficits in SWM performance. Contrary to hypotheses, poorer SWM was not associated with Val allele load. Additionally, COMT generally did not moderate the relations between SWM and negative schizotypy. The findings support the idea that the neurodevelopmental vulnerability for schizophrenia is expressed across a continuum of impairment referred to as schizotypy, the construct validity of a multidimensional model of schizotypy, and the use of psychometric screening inventories as promising tools to help understand the etiology and development of schizophrenia.

THE IMPACT OF CATHECOL-O-METHYL TRANSFERASE ON WORKING MEMORY IN PSYCHOMETRICALLY IDENTIFIED SCHIZOTYPY

by

Jessica A. Kaczorowski

A Dissertation Submitted to
the Faculty of The Graduate School at
The University of North Carolina at Greensboro
in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

Greensboro
2012

Approved by

_____
Committee Chair

APPROVAL PAGE

This dissertation has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

Committee Chair _____
Thomas R. Kwapil

Committee Members _____
George Michel

_____
Michael Kane

_____
Rosemery Nelson-Gray

_____
Date of Acceptance by Committee

_____
Date of Final Oral Examination

ACKNOWLEDGMENTS

I would like to thank my advisor, Dr. Thomas Kwapil, for his guidance and valuable contribution to my development as a researcher. I am also grateful to Dr. Walter Salinger for allowing me to use his data for my dissertation. In addition, I would like to thank my committee members, Drs. Michel, Kane, and Nelson-Gray for their helpful feedback on my research projects. Thank you also to the Kwapil lab members and Taylor Smith for their helpful comments on previous drafts of this manuscript. Lastly, thank you to the participants who took part in this study.

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER I

INTRODUCTION

Patients with schizophrenia and non-clinical schizotypes often exhibit impairment in working memory, which is presumed to be influenced by prefrontal dopamine availability largely controlled by Catechol-O-Methyl transferase (COMT). Current neurodevelopmental models posit that the vulnerability for schizophrenia is expressed across a dynamic continuum of clinical and subclinical impairment referred to as schizotypy. The present study examined the relations and interactions between COMT, spatial working memory (SWM), and psychometrically identified positive and negative schizotypy in a nonclinically ascertained sample of young adults.

Current etiological models conceptualize schizophrenia as a neurodevelopmental disorder[1] (Fatemi & Folsom, 2009; Rapoport et al., 2005; Andreasen, 1999; Meehl, 1990; Weinberger, 1987). The neurodevelopmental hypothesis posits that the liability for schizophrenia arises from neural dysmaturation – a subtle disruption in brain development that begins in the prenatal period with full blown clinical expression usual occurring in late adolescence or early adulthood (Andreasen, 1999). Neural dysmaturation does not necessarily lead to schizophrenia, but rather is expressed across a

[1] The etiology of schizotypy and spectrum disorders involves a process of disrupted neural development. However, it has been suggested that negative symptom schizophrenia, as well as the consequences of the disorder, may result in neurodegeneration in patients with an unremitting course of illness (Jarskog, Gilmore, & Lieberman, 2004).

continuum of impairment referred to as schizotypy (Meehl, 1990). This formulation suggests that schizophrenia and schizophrenia-spectrum disorders can be best conceptualized as the most severe manifestations of illness along the schizotypy continuum. Thus, neural dysmaturation appears to be necessary, but not sufficient, for the development of full-blown schizophrenia, and is expressed across the schizotypy continuum.

The process of neural dysmaturation is presumed to result from the interaction of multiple risk factors including genetic inheritance, gene expression, pre- and peri-natal insults, and other biopsychosocial stressors. Although neural dysmaturation occurs across development, there are several critical periods in which disruptions in neural development markedly heighten the risk for schizotypy, and thus schizophrenia (e.g., Cannon et al., 2003). These include disruptions in crest cell migration during the second trimester in utero, perinatal complications, and disruptions in the timing and nature of synaptic pruning.

A major consequence of neural dysmaturation is the finding of neuroanatomical abnormalities in the prefrontal cortex (e.g., Andreasen et al., 1996), and the functional deficits reported both in functional magnetic resonance imaging and neuropsychological studies in patients with schizophrenia (e.g., Egan et al., 2001). Evidence points to dysfunction in multiple brain regions connected to the prefrontal cortex, including the cerebellum, striatum, thalamus, temporal cortex, and parietal cortex (Weinberger et al., 2001), suggesting that neural dysmaturation can best be understood as an expression of mal-distributed brain circuitry that leaves an individual vulnerable for schizophrenia.

Schizotypy

Schizotypy represents the expression of the neurodevelopmental vulnerability for schizophrenia (Meehl, 1990). Although the majority of people with this vulnerability will never decompensate into clinical schizophrenia[2], they often exhibit mild or transient features of the disorder including cognitive, emotional, and biobehavioral symptoms. Thus, schizotypy is expressed along a dynamic continuum ranging from relative psychological health to subclinical deviance to schizophrenia-spectrum personality disorders to full-blown schizophrenia. Schizotypy is multidimensional in nature, with positive and negative schizotypy being the most consistently replicated factors (Claridge et al., 1996; Kwapil, Barrantes-Vidal, & Silvia, 2008; Vollema & van den Bosch, 1995). Positive schizotypy reflects an excess or distortion of normal functions that includes magical thinking and delusions, as well as perceptual illusions and hallucinations. Negative schizotypy refers to a diminution or loss of normal functions such as social anhedonia, affective flattening, alogia, and avolition. The severity of these features can range from subclinical deviance to the debilitating symptoms seen in full-blown schizophrenia.

There is considerable evidence that supports the schizotypy continuum as an expression of neurodevelopmental vulnerability for schizophrenia. Patients with schizophrenia often exhibit mild and transient signs of the disorder long before they decompensate (e.g., Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Walker,

[2] Meehl (1990) suggested that about 10% of the population is schizotypic and that about 10% of schizotypes will decompensate into schizophrenia (neatly arriving at the 1% lifetime prevalence rate for schizophrenia). Meehl's conjectures were not empirically derived; however, subsequent taxometric analyses have supported his estimates (e.g., Horan, Blanchard, Gangestad, & Kwapil, 2004; Lenzenweger & Korfine, 1992).

Savoie, & Davis, 1994). Compensated relatives of patients with schizophrenia (who are presumed to share genetic liability) often exhibit signs of schizotypy (e.g., Cannon et al., 1994; Erlenmeyer-Kimling et al., 1993). Likewise, putative schizotypes identified by clinical status or psychometric inventories exhibit similar patterns of cognitive and biobehavioral deficits (e.g., impairment in sustained attention, dermatoglyphic anomalies, and neurological soft signs) as patients with schizophrenia (e.g., Bergida & Lenzenweger, 2006; Chok, Kwapil, & Scheuermann, 2005; Kaczorowski, Barrantes-Vidal, & Kwapil, 2009), albeit to a lesser degree.

Taken together, the evidence suggests that the schizotypy continuum is a promising construct from which to study the neurodevelopment of schizophrenia. In addition, the identification and study of nondisordered schizotypes: 1) avoids confounds associated with the catastrophic sequelae of schizophrenia itself (such as hospitalization, medication, and social stigma); 2) should enhance our understanding of the etiology and development of schizophrenia- spectrum disorders, including the identification of risk and protective factors; and 3) is essential for the development and implementation of prophylactic treatment interventions.

Psychometric identification of schizotypy has reliably predicted the development of schizophrenia symptoms and spectrum disorders at follow-up assessments. For example, Chapman et al. (1994) re-interviewed 95% of 534 putatively schizotypic and control participants at a ten-year follow-up assessment. They found that participants initially identified by the Magical Ideation (Eckblad & Chapman, 1983) and Perceptual Aberration (Chapman, Chapman, & Raulin, 1978) Scales had higher rates of psychosis

compared to control participants at the follow-up assessment. Moreover, participants who were identified by the scales at the initial assessment, but did not develop psychosis, still displayed more schizotypal, paranoid, and psychotic-like symptoms compared to the control group at the follow-up assessment. Likewise, Kwapil (1998) found that 24% of participants identified by the Revised Social Anhedonia Scale (Eckblad, Chapman, Chapman, & Mishlove, 1982) compared to 1% of the control participants exhibited schizophrenia-spectrum illnesses at the ten-year follow up assessment.

Schizophrenia, Schizotypy, and Working Memory

The process of neural dysmaturation results in abnormalities in the prefrontal cortex. Animal and human studies suggest that working memory processes are controlled by the neural circuitry of the prefrontal cortex, particularly the dorsolateral prefrontal cortex (e.g., Goldman-Rakic, 1994; Goldman-Rakic, Muly, & Williams, 2000; Goldman-Rakic & Selemon, 1997). Baddeley (1986) conceptualized working memory as a system involving both processing and storage components that maintain access to mental representations. Engle and Kane (2004) argued that attentional control processes are at the core of working memory capacity. Like Engle and Kane (2004), Park and colleagues emphasize maintaining mental representations active above threshold and under the focus of attention, especially during distractions, as a key component of working memory (e.g., Lee & Park, 2005). This definition of working memory will be adopted throughout this proposal.

Park and Holzman (1992) were the first to document working memory deficits in patients with schizophrenia. Following this, numerous studies and meta-analyses (e.g.,

Forbes, Carrick, McIntosh, & Lawrie, 2009; Lee & Park, 2005) reported working memory deficits in patients with schizophrenia. In a meta-analysis of 124 studies, Lee and Park (2005) reported that: 1) working memory deficits occur in schizophrenia; 2) working memory deficits are not domain specific; however, patients show more consistent impairments in visual-spatial working memory compared to verbal working memory tasks; and 3) increasing delay time does not increase working memory deficits beyond those seen after one second. Forbes et al. (2009) built upon this meta-analysis and demonstrated that working memory deficits are not due to differences in intellectual ability between patients with schizophrenia and healthy control participants. Moreover, several researchers define working memory deficits as a core feature of schizophrenia (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997; Goldman-Rakic, 1994).

Numerous tasks are used to assess working memory in patients with schizophrenia including the N-back Task (e.g., Gevins et al., 1996), Oculomotor Delayed Response Task, working memory subscales from the Wechsler Adult Intelligence Scale (e.g., Wechsler, 1997), the failure to maintain set index from the Wisconsin Card Sorting Task (e.g., Harris, 1988), and the SWM task (Owen, Downes, Sahakian, Polkey, & Robbins, 1990) from the Cambridge Neuropsychological Test Battery (CANTAB). Although all of these tasks are useful for examining working memory processes, the SWM task from the CANTAB has several notable strengths. First, the CANTAB battery can be used in both humans and rodents (Geyer, 2008). Secondly, neuroanatomical and neurofunctional studies of the SWM task indicate that it draws upon resources from the dorsolateral prefrontal cortex (e.g., Owen, Doyon, Petrides, & Evans, 1996; Owen,

Evans, & Petrides, 1996) and correlates with antisaccade errors (e.g., Hutton et al., 2004). Therefore, this proposal and literature review will focus on the CANTAB SWM task.

A large literature demonstrates that patients with schizophrenia make significantly more errors than healthy control participants on the CANTAB SWM task (Badcock, Michiel, & Rock, 2005; Cocchi et al., 2009; Hutton et al., 2004; Hutton et al., 1998; Joyce et al., 2002; Joyce, Hutton, Mutsatsa, & Barnes, 2005; Pantelis et al., 1997; Pantelis et al., 2009; Tyson, Laws, Roberts, & Mortimer, 2005). Several studies indicated that the magnitude of the difference in errors between patients and healthy control participants increases as difficulty level rises (e.g., Hutton et al., 1998; Joyce et al., 2002; Pantelis et al, 1997). In addition, patients with schizophrenia perform significantly worse on this task than patients with bipolar disorder (Badcock et al., 2005), Parkinson's disease, frontal lobe lesions, and temporal lobe/amygdalo-hippocampal lesions (Pantelis et al., 1997), but not patients with Alzheimer's disease (Gabrovska-Johnson et al., 2003). Performance on the SWM task does not appear to be impacted by medication (e.g., Barrett, Bell, Watson, & King, 2004), substance use (e.g., Barnes, Mutsatsa, Hutton, Watt, & Joyce, 2006; McCartan et al., 2001), or change across a 9-month interval (Tyson et al., 2005).

Although patients with schizophrenia consistently show impairment on the CANTAB SWM task, the majority of studies failed to examine the relation of positive and negative symptoms with performance on this task. However, several studies reported a relation between negative symptoms (Pantelis et al., 2004; Pantelis, Stuart, Nelson, Robbins, & Barnes, 2001; Pantelis et al., 2009; Wood et al., 2003), one study found a

weak association with positive symptoms (Elliot, McKenna, Robbins, & Sahakian, 1998), and others found null results (Cocchi et al., 2009; Joyce et al., 2002; Tyson et al., 2005). Several researchers (Weinberger, 1987; Weinberger et al., 2001) suggest that negative symptoms reflect prefrontal neuronal impairment. For example, Callicott et al. (2000) found that decreased N-acetyl aspartate concentration in the dorsolateral prefrontal cortex (lower levels indicate neuronal pathology) was related to increased negative, but not positive, symptoms and explained 25% of the variance in negative symptoms in patients.

Consistent with a continuum model of schizotypy, unaffected, biological relatives of patients with schizophrenia tend to demonstrate working memory deficits compared to healthy control participants (Conklin, Curtis, Katsanis, & Iacono, 2000; Diwadkar, Montrose, Dworakowski, Sweeney, & Keshavan, 2006; Egan et al., 2001; Johnson et al., 2003; Myles-Worsley & Park, 2002; Park, Holzman, & Goldman-Rakic, 1995). O'Conner et al. (2009) are the only group to have used the CANTAB SWM task to examine this relationship between genetically high-risk individuals and healthy control participants. Although they found no differences between the groups on this task, the results are uninterpretable since the groups differed on IQ and the authors inappropriately used this variable as a covariate in the analyses.

Working memory deficits are also reported in schizotypic individuals identified by clinical status (i.e., in the prodromal phase or schizophrenia or diagnosed with schizotypal personality disorder). For example, Wood et al. (2003) reported that two "ultra high-risk" groups from the Edinburgh High Risk Study, one that developed psychosis and one that did not, performed significantly worse on the CANTAB SWM

task compared to healthy control participants. Moreover, the ultra high-risk psychotic group generally performed worse than the non-psychotic risk group on all cognitive tasks, although these finding did not reach significance. In addition, only the ultra high risk-psychotic group demonstrated a significant relationship between performance on the CANTAB SWM task and negative symptoms. Bartok et al. (2005) reported that pre-psychotic patients scored significantly lower on the CANTAB SWM task compared to healthy control participants; however, they did not assess the relation of positive and negative symptoms with working memory.

A growing literature has examined the relation between working memory performance and psychometrically identified schizotypy; however, to date, no published study has utilized the CANTAB SWM task. Park, Holzman, and Lenzenweger (1995) reported that individuals who scored at least 2 standard deviations above the mean on the Perceptual Aberration scale (presumed to tap positive schizotypy) performed significantly worse on an oculomotor delayed response task compared to individuals who scored no higher than .5 standard deviations above the mean on that scale. However, when using the Schizotypal Personality Questionnaire (Raine, 1991), Park and McTigue (1997) reported a trend for the association of poorer performance on the delayed response task with the negative symptom factor and a significant association with the "no close friends," a subscale of the negative symptom factor.

Tallent and Gooding (1999) attempted to replicate and extend the findings by Park et al. (1995) by including an additional measure of positive schizotypy, the Magical Ideation scale, and a measure of negative schizotypy, the Revised Social Anhedonia

Scale . They reported that the social anhedonia group (those who scored 2 standard deviations above the mean on the scale) and the perceptual aberration/magical ideation group (those who score 2 standard deviations on at least one of the scales) performed significantly worse than healthy control participants, but did not differ from each other on working memory performance as assessed by a delayed response working memory task. However, the social anhedonia group had slower reaction times than either group. Importantly, the social anhedonia score accounted for significant variance in working memory task accuracy over and above the perceptual aberration/magical ideation score.

Using structural equation modeling, Smyrnis et al. (2007) reported that only negative and paranoid schizotypy (with loadings from the Schizotypal Personality Disorder Questionnaire) were related to cognitive performance accuracy based upon verbal and spatial versions of the N-back task (Gevins et al., 1996), Ravens Progressive Matrices total score (Raven, 1982), and Continuous Performance Task – Identical Pairs version d-prime index (Cornblatt, Lenzenweger, & Erlenmeyer-Kimling, 1989; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988). Specifically, higher negative schizotypy scores were related to poorer cognitive performance whereas higher paranoid schizotypy scores were related to better cognitive performance. However, it is difficult to draw conclusions from this study regarding working memory because the composite also included non-working memory tasks. Moreover, the structural equation model is largely uninterpretable due to the use of unstandardized coefficients and concerns related to the authors' *post hoc* decision to drop latent factors from the model.

Kerns and Becker (2008) reported that a disorganized schizotypy group, that included individuals who score 1.96 standard deviations above the mean on the Cognitive Slippage scale (Miers & Raulin, 1987), performed more poorly than control participants (individuals who scored no higher than .5 standard deviations above the mean on the scale) on a 3-back working memory task. In contrast, using a backward elimination regression approach, Matheson and Langdon (2008) reported that lower scores on letter-number sequencing were related to higher scores on the cognitive/perceptual and interpersonal factors of the Schizotypal Personality Disorder Questionnaire. However, it is difficult to interpret these results given that the statistical approach was not based on *a priori* hypotheses. Finally, a few studies reported no relation between working memory performance and psychometrically identified schizotypy (Lenzenweger & Gold, 2000; Noguchi, Hori, & Kunugi, 2008).

Catechol-O-Methyl transferase

The COMT gene is located on chromosome 22 at band q11.2. COMT promoters (P1 and P2) control transcription of two different messenger ribonucleic acids (Chen et al., 2004; Tenhunen, Salminen, Jalanko, Ukkonen, & Ulmanen, 1993). P1 encodes soluble COMT and P2 encodes membrane bound COMT. Soluble COMT is expressed in the liver, blood, and kidneys, whereas membrane bound COMT is expressed predominately in prefrontal regions of the brain. They differ in substrate affinities and capacities, with membrane bound COMT having a 10-fold greater affinity (despite a smaller capacity) for catecholamines such as dopamine (Lotta et al., 1995; Tunbridge, Harrison, & Weinberger, 2006); therefore, membrane bound COMT is involved in

metabolizing dopamine found in prefrontal regions of the brain. Henceforth, this document will refer to the COMT Val158Met polymorphism when discussing COMT.

COMT contains a functional polymorphism, a G → A substitution at exon 4, which results in a Valine (Val) to Methionine (Met) amino acid substitution at codon 158 in membrane bound-COMT (Lachman et al., 1996). The enzyme activity of Val (the high activity allele) is ~40% higher than that of Met (the low activity allele) at 37 degrees Celsius in postmortem human dorsolateral prefrontal cortex (Chen et al., 2004). Thus, Val homozygotes (i.e., those with two copies of the same allele) have increased COMT activity in their prefrontal cortex compared to Met homozygotes, with Val/Met heterozygotes (i.e., those with one copy of each allele) falling in the middle because alleles are codominant (Chen et al., 2004; Tunbridge et al., 2006).

Although synaptic dopamine transporters have a much higher affinity towards dopamine than COMT, they are found in low quantities in the prefrontal cortex and do not impact extracellular dopamine levels (Chen et al., 2004; Lewis et al., 2001; Weinberger et al., 2001). Therefore, COMT is largely responsible for dopamine metabolism in the prefrontal cortex (Chen et al., 2004; Weinberger et al., 2001). This presumably results in Val homozygotes having less available dopamine in prefrontal regions of the brain compared to Met homozygotes, with heterozygotes falling in the middle (Chen et al., 2004). The notion that COMT is critical for metabolizing dopamine in the prefrontal cortex is supported by animal studies. For example, Tunbridge et al. (2004) found that a COMT inhibitor, tolcapone, doubled dopamine, but not noradrenaline levels, in the rat prefrontal cortex when catecholamine efflux was induced. In addition,

Gogos et al. (1998) reported that male COMT knockout mice showed a two- to three-fold increase in frontal dopamine levels, but no dopamine changes in other regions.

Since COMT is expressed in prefrontal regions of the brain, and COMT genotype differentially influences COMT enzymatic activity and thus prefrontal dopamine availability, one would expect COMT genotype to differentially impact prefrontally mediated cognitive processes such as working memory. Although the literature is inconsistent regarding this association (e.g., Egan et al. 2001; Barnett et al., 2007, Barnett et al., 2008; Liao et al., 2009; Wishart et al., 2011), there is considerable theoretical and empirical evidence that suggests that COMT plays a small but significant role in moderating working memory processes. Study characteristics such as task and sample variability and sample size likely contribute to the inconsistent findings in the literature. Note that COMT is just one source of variation that contributes to working memory performance and it would be naïve to assume that the differences in complex phenotypes such as working memory can be perfectly mapped to COMT.

Schizophrenia, schizotypy, and COMT. Linkage studies have identified COMT as a susceptibility gene for schizophrenia (e.g., McGuffin, Tandon, & Corsico, 2003; Owen, Williams, & O'Donovan, 2004). However, the results from individual studies are largely inconclusive (Daniels et al., 1996; Fan et al., 2005; Glatt, Faraone, & Tsuang, 2003; Kremer et al., 2003; Okochi et al., 2009; Sazci et al., 2004; Shifman et al., 2002). A few studies (Egan et al., 2001; Kunugi et al., 1997) and meta-analyses (e.g., Glatt et al., 2003) suggest that the Val allele represents a small, but reliable risk factor for schizophrenia. In addition, Shifman et al. (2002) found the Val allele to be associated

with schizophrenia in a large sample of Ashkenazi Jews. This relationship was even stronger when examining a COMT haplotype, which included the Val allele.

Few studies have assessed whether COMT is related to the clinical presentation of patients with schizophrenia. Strous et al. (2006) found no relationship between COMT genotype and clinical symptoms in patients with schizophrenia, whereas another found an association between the Val allele and negative symptoms (i.e., Wang et al., 2010) and others reported and relation with positive symptoms (Goghari & Sponheim, 2008; Molero, Ortuno, Zalacain, & Patino-Garcia, 2007). Furthermore, Han et al. (2006) reported that individuals with schizophrenia who were homozygous for the Val allele displayed more inappropriate affect than those homozygous for the Met allele. However, the Met allele has also been associated with aggressive (Han et al., 2006; Lachman, Nolan, Mohr, Saito, & Volavka, 1998; Strous et al., 2003) and suicidal behavior (Nolan et al., 2000) in patients with schizophrenia.

Consistent with the continuum model of schizotypy, several studies have examined the impact of COMT in individuals identified as part of the schizotypy continuum by consanguinity or psychometric screening inventories. Docherty and Sponheim (2008) found that relatives of patients with schizophrenia who were homozygous for the Val allele had the highest scores on the Social Anhedonia and Physical Anhedonia Scales (Chapman, Chapman, & Raulin, 1976) compared to healthy controls; however, COMT was unrelated to scores on the Magical Ideation or Perceptual Aberration Scales. In addition, there was no relation between COMT and relatives of patients with bipolar disorder or healthy controls. However, Schurhoff et al. (2007) found

that scores on the positive and negative dimension of the Schizotypal Personality Questionnaire in relatives of patients with schizophrenia were both related to Val homozygosity, but not Val/Met heterozygosity or Met homozygosity. Moreover, there was a stepwise relation such that Val homozygotes had the highest scores on these dimensions and Met homozygotes had the lowest scores, with heterozygotes falling in the middle.

Stefanis and colleagues (Avramopoulos et al., 2002; Smyrnis et al., 2007; Stefanis et al., 2004) used a sample of male Greek conscripts to examine the relation of COMT with scores on the Schizotypal Personality Questionnaire. Avramopoulos et al. (2002) reported that higher total scores were related to COMT in a step-wise fashion with Val homozygotes scoring the highest, Met homozygotes scoring the lowest, and Val/Met heterozygotes falling in the middle. These researchers also administered the Perceptual Aberration Scale and found a slightly different order – Val homozygotes had the highest scores, followed by Met homozygotes, and then Val/Met heterozygotes. Building upon Avramopolous et al. (2002), Stefanis et al. (2004) reported that Val allele load was increasingly associated with the negative and disorganized dimensions of the Schizotypal Personality Questionnaire. Finally, Smyrnis et al. (2007) found that Val homozygosity was significantly related to higher scores on the negative and disorganized factors, whereas Val/Met heterozygosity and Met homozygosity was significantly related to the paranoid factor. In addition, Val homozygotes had significantly higher scores on many of the Symptom Check List–90 (Derogatis, 1993) subscales compared to Val/Met heterozygotes or Met homozygotes. Due to the concerns noted previously, however, these

results should be interpreted cautiously. In contrast to these results, Sheldrick et al. (2008) found that Met homozygosity was associated with increasing scores on the disorganized dimension of the Schizotypal Personality Questionnaire – Brief Version.

A few studies failed to find associations between COMT and schizotypy. For example, Ettinger et al. (2006) found no relation using the Rust Inventory of Schizotypal Cognitions (Rust, 1989). However, the validity of the Rust Inventory as a measure of schizotypy has not been well established (Chapman, Chapman, & Kwapil, 1995). In addition, Ma et al. (2007) did not find a relation between COMT and the Schizotypal Personality Questionnaire in a large sample of healthy Chinese participants after correction for multiple comparisons. The authors noted that population stratification effects may have impacted their results.

COMT and Working Memory in Schizophrenia and Schizotypy

Several studies (e.g., Egan et al., 2001; Goldberg et al., 2003; Barnett et al., 2007; Wishart et al., 2011; Wirgenes et al., 2010; Bilder et al., 2002; Gallinat et al., 2003), but not all (e.g., Barnett et al., 2008), have shown that performance on working memory tasks and other tasks presumed to draw upon prefrontal resources is systematically related to COMT genotype in adults. In a seminal study, Egan et al. (2001) examined the relation between COMT and working memory performance. Patients with schizophrenia and their unaffected biological siblings underwent functional magnetic resonance imaging while performing an N-back task. Patients and siblings were matched for task performance. Genotype groups within the patients and siblings did not differ on performance accuracy; however, Met load predicted prefrontal physiological efficiency such that Met

homozygotes were more efficient than Val homozygotes with heterozygotes falling in the middle, when matched for overall accuracy. This pattern of efficiency was similar in both the sibling and patient groups; however the authors did not indicate whether the level of efficiency was statistically different between the groups. These data suggest that the impact of COMT on working memory processes is not specific to schizophrenia, but rather a generalizable human characteristic (Egan et al., 2001; Weinberger et al., 2001).

Mattay et al. (2003) demonstrated how increasing dopamine levels either had a favorable or unfavorable impact on working memory performance based on COMT genotype. Specifically, they examined the effect of COMT on prefrontal efficiency (as assayed by functional magnetic resonance imaging) during the N-back Test both on and off amphetamines (which are presumed to increase dopamine neurotransmission). Mattay et al. found that, compared to the placebo condition, the amphetamine condition resulted in Val homozygotes showing enhanced prefrontal efficiency and decreased reaction time at all levels of task difficulty on the N-back Test; however, it did not influence performance accuracy. In contrast, the amphetamine condition had no effect on the prefrontal efficiency of Met homozygotes in low to moderate difficultly conditions, but caused less efficient processing, a decrease in performance, and an increase in reaction time at high difficultly conditions. Val/Met heterozygotes showed consistent performance across task difficulty, but improved prefrontal efficiency in the amphetamine condition. These data support the idea that prefrontal dopamine levels, which are regulated by COMT genotype, impact working memory performance and that there is an "optimal range" of dopamine availability.

Surprisingly, Smyrnis et al. (2007) is the only study to examine the relation between COMT, working memory, and schizotypy. They found that increasing Val load was associated with a "dose dependent increase" in the factor loading between negative schizotypy and the cognitive performance accuracy composite, such that higher scores on the negative schizotypy factor were associated with lower cognitive performance accuracy. As mentioned previously, however, the results are largely uninterpretable due to the inclusion of non-working memory tasks in the composite, the use of unstandardized coefficients in the structural equation model, and concerns related to the exclusion of additional latent factors.

Goals and Hypotheses of the Present Study

The present study sought to extend the current literature by examining the relations of COMT and working memory with psychometrically identified positive and negative schizotypy in a nonclinically ascertained sample of young adults. Only one study (Smyrnis et al., 2007) has examined the relation between COMT and cognitive performance in psychometrically identified schizotypy and the results are largely uninterpretable. The following hypotheses were offered:

1. Higher scores on negative schizotypy would be related to increasing Val load; however, no hypothesis was offered with positive schizotypy due to inconsistent findings in the literature.
2. Negative, but not positive schizotypy, would be associated with poorer performance on the SWM task.
3. Poorer performance on SWM would be associated with Val allele load.

4. COMT would moderate the relation between working memory and negative schizotypy, with Val allele load being associated with more impaired performance on this task.

CHAPTER II

METHOD

Participants

The sample was drawn from an archival dataset of 407 college undergraduates who were enrolled in general psychology courses at the University of North Carolina at Greensboro (UNCG) from January 2007 to May 2008. From this initial sample, a total of 29 participants had unusable schizotypy data due to their scores on an infrequency scale (Chapman & Chapman, 1983), 58 participants did not have COMT genotyping data, and 1 participant did not have SWM data. In addition, 8 participants were excluded due to being statistical outliers on the schizotypy measures. In order to maximize power, different samples were used from the original sample of 407 participants. This resulted in a sample of 312 participants to examine the relation between COMT and positive and negative schizotypy, 369 participants to assess the relation between positive and negative schizotypy and SWM, and 311 participants to examine the impact of COMT on SWM in positive and negative schizotypy.[3] Demographic data is reported for the largest sample (*n*

[3] All three samples came from the overall sample of 407 participants. A total of 312 participants were used to examine the relation between COMT and schizotypy (29 participants were dropped due to unusable schizotypy data, 58 did not have COMT data, 8 participants were outliers). A total of 369 participants were used to examine the relation between COMT and SWM (29 participants were dropped due to unusable schizotypy data, 1 participant had no SWM data, and 8 participants were outliers). A total of 311 participants were used to examine the impact of COMT on SWM in positive and negative schizotypy (29 participants were dropped due to unusable schizotypy data, 58 did not have COMT data, 1 had no SWM data, and 8 participants were outliers).

= 369); however, there were no significant differences in terms of demographic variables between the largest sample and the other samples.

The mean age of the sample at the time of the assessment was 19.4 (SD = 2.88, range = 17 – 41) years. The sample consisted of 49 Caucasian males, 186 Caucasian females, 11 African-American males, 83 American-American females, 3 Asian males, 7 Asian females, 12 Hispanic females, 6 males and 11 females who were classified as other (i.e., not Caucasian, African-American or Asian, or Hispanic), and 1 female who did not specify her race. This composition is consistent with the university demographics.

Materials

Schizotypy Questionnaires

The schizotypy questionnaires included the Perceptual Aberration, Magical Ideation, Physical Anhedonia, and Revised Social Anhedonia Scales, and an infrequency scale. The Perceptual Aberration Scale contains 35 items that tap psychotic-like perceptual experiences and bodily distortions. The Magical Ideation Scale consists of 30 items that assess belief in improbable or invalid causality. The Revised Social Anhedonia Scale includes 40 items that tap asociality and indifference towards interpersonal relationships. The Physical Anhedonia Scale is comprised of 61 items that assess deficits in sensory and aesthetic pleasure. The Perceptual Aberration and Magical Ideation Scales assess positive schizotypy, and the Physical Anhedonia Scale taps negative schizotypy. The Revised Social Anhedonia Scale appears to assess both positive and negative schizotypy. Exploratory and confirmatory factor analyses of the four scales reliably produce two factors, labeled positive and negative schizotypy, that account for

approximately 80% of the variance in the measures (Brown, Silvia, Myin-Germeys, Lewandowski, & Kwapil, 2008; Kwapil et al., 2008; Lewandowski et al., 2006). Participants were assigned positive and negative schizotypy dimensional scores, based upon factor loadings derived from a sample of 6,137 college students (Kwapil et al., 2008). The infrequency scale consists of 13 items and is designed to screen out participants who respond in a random or "fake-bad" manner. Participants who endorsed more than two of these items were omitted from further study. The schizotypy questionnaires are widely used and have good internal consistency (.82-.92). See Appendix A for a copy of the schizotypy questionnaires.

Cambridge Neuropsychological Test Battery (CANTAB) Spatial Working Memory (SWM)

The CANTAB (Owen et al., 1990) battery includes a total of 22 computerized tasks designed to measure various cognitive processes. It has been used extensively to examine various cognitive processes in patients with schizophrenia. The SWM task from the CANTAB was used in the present study. The SWM task measures a participant's ability to retain and manipulate spatial information in memory. The goal of the task is for participants to search a set of boxes presented on the computer screen for a series of blue tokens. The participant determines the search order. Participants are instructed that boxes that already contained a blue token will never contain another blue token; therefore, they should not touch those boxes again. The task takes approximately eight minutes to complete.

The SWM task begins with a sample trial in which the examiner explains the task to the participant. The sample trial consists of three boxes to search through. Next, the participant is administered a practice set consisting of three trials with three boxes each. Note that a set consists of a predetermined number of trials and a trial consists of the searches needed to fill the column on the right side of the computer screen with the blue tokens. The boxes remain in the same position between trials and change positions between sets. In other words, the participant sees the same display of boxes on the computer screen for each set; however, the display of boxes on the computer screen changes between sets. If the participant chooses a box that has already contained a blue token during the practice trials, the examiner reminds the participant that the computer will never hide the blue token in that box again. The test consists of three sets: four trials with four blocks each, four trials with six blocks each, and four trials with eight blocks each. Note that the color of the boxes changes between trials.

The SWM task contains several outcome measures. SWM between errors occur when a participant chooses a box that already contained a blue token between test trials. SWM within errors occur when a participant returns to a box that did not contain a blue token within a trial. SWM double errors are defined as errors that could be considered either between or within errors. The SWM task also yields a total error count for each of the domains (between, within, and double). In addition, the SWM task yields several latency measures including: 1) mean time to first response for trials with 4, 6, and 8 boxes; 2) mean time to last response for trials with 4, 6, and 8 boxes; and 3) mean token search-preparation time for trials with 4, 6, and 8 boxes. Owen et al. (1990) indicated that

starting with a specific box and returning to that box once a blue token has been identified is an efficient strategy to employ between sets within a trial. Lower scores reflect superior strategy.

Genotyping

All participants were genotyped for COMT Val158Met. Two DNA buccal swabs (Isohelix swabs; Boca Scientific) were used to collect DNA by rubbing the inside of each participant's cheeks with a swab for 30 seconds prior to placing it in a collection tube provided with the Isohelix kit. Nuclear DNA was extracted from the buccal swabs following the Isohelix procedures, at the Molecular Biology Core Laboratory at UNCG. A random set of samples was subjected to manual SNP genotyping using an Amersham sequencing unit and manufacturer's protocols. Spectrophotometer readings (A260/280) were taken of all the samples to ensure the relative purity of the DNA. The extracted DNA samples were then stored at -20 degrees C and sent as a batch to GeneSeek Inc (Lincoln, NE), where single nucleotide polymorphism (SNP) genotype, including the one responsible for COMT Val158Met (rs4680), were determined for each subject. The random sample of SNP genotypes produced in the Core Laboratory were compared with those reported in the GeneSeek database to ensure that the genotyping was accurate (in terms of chemistry and sample identification). In every case, the genotype determined by GeneSeek matched the one obtained with the Amersham method. The distribution of the genotypes obtained for COMT Val158Met for the 312 subjects (Met/Met = 71; Val/Met = 143; Val/Val = 98) was consistent with Hardy-Weinberg equilibrium ($p > .05$).

Procedures

Participants volunteered to take part in the proposed study through a web-based sign-up system. Participants completed the assessments, as well as a larger battery of tasks, at an individual testing session. Participants were administered the tasks in the following order: DNA sampling, CANTAB motor screening, CANTAB SWM task, and the schizotypy questionnaires. Participants who had corrected vision or hearing needed to have their correction with them to take part in the study. Consent was obtained from each participant.

CHAPTER III

RESULTS

Statistical analyses were conducted using MPlus version 6.1 (MPlus 6.1, 2010) and SPSS version 18 (SPSS, 2009). A series of preliminary analyses were conducted to examine the nature of the schizotypy, SWM, and COMT data.

Descriptive Statistics and Correlations

Table 1 presents the mean, standard deviation, minimum, maximum, skew, and kurtosis for positive schizotypy, negative schizotypy, COMT, and each SWM variable. Note that all SWM latency measures (measured in milliseconds) were rescaled by dividing each value by 1000. There were no significant differences between the samples (n = 369, n = 312, n = 311) in terms of descriptive statistics. Table 2 presents a zero-order correlation matrix of all variables. Spearman correlations were used due to the skewed nature of the data.

Schizotypy Data

Participants were assigned positive and negative schizotypy dimensional scores based on a sample of 6,147 college students (Kwapil et al., 2008). Note that the sample included a broad range of scores on the schizotypy dimensions. The skew statistic and qualitative inspection of each distribution revealed that the distributions for positive and negative schizotypy were highly skewed in the positive direction (see Table 1). Using the recommendations of Fidell and Tabachnick (2003), positive and negative schizotypy

were transformed by taking the log of each variable. All subsequent analyses were computed using the transformed values for positive and negative schizotypy. The distributions for both positive and negative schizotypy factors were unimodal and correlated modestly, $r = .22$, $p<.001$. There were no significant differences between the samples ($n = 369$, $n = 312$, $n = 311$) in terms of positive and negative schizotypy.

Relation of Schizotypy and COMT Val158Met

As hypothesized, ANOVAs revealed a significant association of COMT with negative schizotypy, $F(2,309)=6.75$, $p\leq.001$, but not positive schizotypy, $F(2,309)=.07$ (Kaczorowski et al., 2011). Figure 1 presents the COMT group comparisons. Newman-Keuls comparisons indicated that the Val/Val group significantly exceeded the Val/Met and Met/Met groups on negative schizotypy scores, $p<.05$ and $p<.001$, respectively. Linear contrast coding indicated that Val allele load was related to negative schizotypy in an allele-dependent fashion ($p<.001$) and accounted for 4% of the variance in negative schizotypy.

Relation of Schizotypy and SWM

In order to examine the relations of positive and negative schizotypy with SWM outcomes, a series of regression analyses with SWM measures (between, within, double errors, mean time to first response, mean time to last response, mean token search-preparation time, and strategy) as the dependent variables were conducted. The SWM data has a hierarchical structure in which trial type (i.e., 4, 6, or 8 block conditions are level 1 data) is nested within participants (level 2 data). Because trial type was included in the analyses to see whether the relations changed across block conditions, multi-level

modeling was used. Multilevel modeling is a more powerful approach to analyzing nested data compared to the more commonly used unilevel regression analyses (Hox, 2002; Luke, 2004).

The multilevel analyses examined two types of relations between positive and negative schizotypy and SWM. The first set of analyses assessed the direct effects of the level 2 predictors (positive schizotypy, negative schizotypy) on the level 1 criterion (between errors, within errors, double errors, mean time to first response, mean time to last response, and mean token search-preparation time). The second set of analyses examined cross-level interactions of the relations of the level 1 predictor (4, 6, and 8 block conditions) and criterions (SWM performance) with the level 2 variables (positive schizotypy, negative schizotypy). The cross-level interaction analyses tested the effect of the level 2 predictors on the level 1 slopes (slope of condition by SWM performance). Note that the intercept of the slope evaluates the strength of the relations between the level 1 predictor and criterion, independent of the level 2 variables. This provides validation of the SWM assessment such that failing to find a relation between trial type and performance would raise concerns about the validity of the SWM assessment. A lack of cross-level interactions does not mean that there was not a relation between positive and/or negative schizotypy and SWM performance. Rather, a cross-level interaction clarifies the relation to determine if the relation between the level 1 variable changes as a function of the level 2 variable; that is, did the slope of SWM performance across trial type change across levels of schizotypy.

The multi-level analyses were computed using MPLUS version 6.1 (Mplus, 2010). Consistent with the recommendations of Cohen, Cohen, West, and Aiken (2003) and Luke (2004), level 1 predictors were group mean centered and level 2 predictors were grand mean centered. Due to the highly positively skewed nature of the SWM distributions, traditional ordinary least squares linear regression was deemed inappropriate due to the severe violation of normality. Negative binomial regressions were used to analyze SWM data. Negative binomial regression is a generalized linear model that accounts for a highly positively skewed distribution and is used with count data (Agresti, 2007). The negative binomial distribution is unimodal, positively skewed over nonnegative integer values, and unlike a Poisson distribution, does not assume equivalence of the mean and variance. Negative binomial regression is similar to Poisson regression; however, it includes the *D* parameter in the model which allows the variance to be greater than the mean.[4] Analysis of the *D* parameter indicated that the SWM data had negative binomial, rather than Poisson, distributions.

Tables 3 and 4 presents the multi-level regression analyses used to examine the relation between positive and negative schizotypy and SWM. Positive and negative schizotypy were entered at the first step, so the effects of each can be assessed with the other partialed out. Table 3 presents the direct effects of positive schizotypy and negative schizotypy with SWM performance. As expected, negative, but not positive, schizotypy was generally related to SWM outcomes. In particular, negative schizotypy was

[4] Note that a Poisson distribution assumes that the mean and variance are equivalent. However, subject heterogeneity often results in a variance that is larger than the mean, which is called overdispersion. Overdispersion is measured by the dispersion parameter (*D*), which summarizes the extent of overdispersion relative to a Poisson distribution (Agresti, 2007).

significantly associated with increased within and double errors, and slower mean token search-preparation time. Contrary to hypotheses, positive schizotypy was associated with elevated between errors.

Table 4 presents the results from the cross-level interaction analyses, which examined whether positive schizotypy and negative schizotypy moderated the association between trial type (i.e., 4, 6, or 8 block conditions) and SWM domain performance. There were significant relations between the level 1 SWM predictors and criterions. Negative schizotypy moderated these relations for within errors, double errors, mean time to first response, and mean token search-preparation time. Note that traditional simple slopes analyses cannot be performed in MPLUS (P. Silvia, personal communication, May 6, 2011); therefore, the raw data was graphed in HLM 6 (Raudenbush, Bryk, & Congdon, 2004) to aid with the interpretation of cross-level interactions. Because raw data were used, these results should be interpreted cautiously. The graphs suggested that negative schizotypy moderated the association between trial type and SWM performance such that high and low negative schizotypy was unrelated to within and double errors on the hard trials; however, high negative schizotypy was associated with increased within and double errors on the easy trials as well (see Figure 2). In addition, the graphs indicated that negative schizotypy moderated the association between trial type and latency such that high negative schizotypy performed slower as trial type increased (see Figure 3). Positive schizotypy did not moderate any of the relations between the level 1 SWM predictors and criterions.

Does COMT Moderate the Association of Schizotypy and SWM?

Consistent with the aforementioned analyses, multi-level modeling and negative binomial regressions were used due to the nature of the data. Positive and negative schizotypy were entered at the first step as level 2 variables. COMT was entered at the second step as an additional level 2 variable. The COMT X positive schizotypy and COMT X negative schizotypy interaction terms were entered at the third step to examine their effects over-and-above the main effects.

Table 5 presents the direct effects of positive schizotypy, negative schizotypy, COMT, and positive schizotypy X COMT and negative schizotypy X COMT interaction terms with SWM performance. Negative schizotypy was significantly associated with increased within and double errors. Contrary to hypotheses, positive schizotypy was related to increased between errors and COMT was unrelated to any SWM outcomes. The positive schizotypy X COMT and negative schizotypy X COMT interaction terms were generally unrelated to SWM performance. However, there was a significant relation between double errors and the COMT X negative schizotypy interaction. In order to decompose this interaction, the slope for negative schizotypy and double errors was evaluated at each level of COMT: Met/Met genotype: $\gamma = 15.167$ (*SE* = 5.799), $p<.01$; Val/Met genotype: $\gamma = 1.634$ *(SE* = 1.645*), n.s;* Val/Val genotype: $\gamma = 2.002$ (*SE* = 2.169)*, n.s.* This suggests that COMT moderated the relation between negative schizotypy and double errors such that the effect is only seen in individuals with Met/Met genotype. In other words, negative schizotypy was unrelated to double errors for individuals with Val/Val or Val/Met genotypes; however, negative schizotypy had a

significant positive association with double errors for individuals with the Met/Met genotype.

Table 6 summarizes the results from the cross-level interaction analyses, which examined whether COMT, positive schizotypy, negative schizotypy, and the positive schizotypy X COMT, and negative schizotypy X COMT interaction terms moderated the association between trial type (i.e., 4, 6, or 8 block conditions) and SWM domain performance. There were significant relations between all level 1 SWM predictors and criterions. Negative schizotypy moderated these relations for mean time to first response and mean token search-preparation time such that high negative schizotypy performed slower as trial type increased. Finally, the COMT X negative schizotypy interaction was significant. The change in the slope of trial type and double errors across negative schizotypy was evaluated at each level of COMT: Met/Met genotype: γ = -13.594 (*SE* = 5.917), $p<.05$; Val/Met genotype: γ = -2.820 *(SE* = 2.069*),* n.s*;* Val/Val genotype: γ = -0.751 (*SE* = 2.084), n.s.

CHAPTER IV

DISCUSSION

The Schizotypy Framework

Current theoretical models conceptualize schizophrenia as a neurodevelopmental disorder, the vulnerability of which is expressed across a broad continuum of impairment called schizotypy. The schizotypy continuum ranges from relative psychological health to subclinical deviance to schizophrenia-spectrum personality disorders to full-blown schizophrenia. In other words, schizophrenia and schizophrenia-spectrum disorders represent the most extreme expressions of illness along the schizotypy continuum. Schizotypy is also conceptualized as multidimensional in nature, with positive and negative schizotypy being the most consistently replicated dimensions. However, other factors have been proposed such as paranoid and disorganized dimensions (e.g., Stefanis et al., 2004). There are many advantages to the schizotypy model. First of all, it allows us to examine the etiology of schizophrenia relatively untainted by the illness itself. Indeed, factors such as hospitalization, medication, and social stigma undoubtedly confound our ability to understand relevant etiological factors. Secondly, it helps identify risk and protective factors that may impact the possibility of remaining relatively compensated or decompensating into a diagnosable disorder. Finally, the development and success of prophylactic interventions is based on the reliable identification of

individuals vulnerable for developing spectrum disorders. The multidimensional model of schizotypy provides a promising point of entry for developing such treatments.

Several lines of evidence support the use of psychometric screening inventories as promising tools for identifying individuals along the schizoypy continuum. For example, scores on psychometric screening inventories are related to and predict a wide range of factors relevant to the etiology of schizophrenia including genetic, biobehavioral, cognitive, and clinical markers. Moreover, they reliably predict the development of schizophrenia-spectrum disorders in longitudinal studies. However, the psychometric method has been criticized due to the belief that it identifies false positives. This criticism seems to confuse diagnostic-based criterion validation with that of construct validation. Criterion validation is often used in prodromal research when the goal is to identify individuals who will transition into schizophrenia. This is a useful approach for research that focuses on the development and implementation of preventative interventions since transition into a spectrum disorder is often used as an index of treatment success. Construct validation is appropriate in the case of multidimensional schizotypy (consistent with Clairidge or Meehl's conceptualizations) in which the goal is to test predictions about the etiology and expression of schizotypy (across the range of the construct). The construct validation approach is equally interested in milder, transient expressions along the schizotypy continuum – even beyond those associated with schizotypal personality disorder. This involves testing and making predictions about pathology associated with schizophrenia in nondisordered schizotypes. For example, the finding that neurological soft signs are associated with negative, but not positive schizotypy (e.g., Kaczorowski et

al., 2009), supports the construct validity of multidimensional schizotypy. Furthermore, integrating factors from multiple domains (e.g., family history, psychometric screening, subclinical symptoms) should increase our identification of schizotypes at especially high risk for developing a spectrum disorder.

The Present study

The present study aimed to further the validation of the multidimensional construct of schizotypy by investigating the relations and interactions between COMT, SWM, and psychometrically identified positive and negative schizotypy. This is the first study to assess the relationship between COMT and psychometric inventories aimed at assessing the broader schizotypy continuum, as opposed to schizotypal personality disorder traits (i.e., the Schizotypal Personality Questionnaire) in nonclinical samples. Additionally, no published study has utilized the CANTAB SWM task in a sample of psychometrically identified schizotypy. Finally, the present study builds upon and extends the current literature by assessing multiple dimensions of schizotypy, using advanced statistical techniques appropriate for the nature of the data, and overcoming the limitations of Smyrnis et al. (2007) by employing *a priori* hypotheses and appropriate statistics to examine the interaction of SWM, COMT, and schizotypy.

As hypothesized, negative, but not positive, schizotypy was associated with Val allele load in an increasing allele-dependent fashion. Additionally, negative, but not positive, schizotypy was generally related to SWM outcomes including increased within and double errors, as well as a longer mean time to first response and mean token search preparation time. However, positive schizotypy was associated with increased between

errors. Contrary to hypotheses, COMT was unrelated to SWM performance. The COMT X positive schizotypy and COMT X negative schiztoypy interactions were generally unrelated to SWM outcomes; however, the COMT X negative schizotypy interaction was associated with double errors. These results are generally consistent with the schizophrenia literature and support the multidimensional framework of schizotypy. Note that the psychometric screening inventories did not inquire about SWM deficits – so the results are not simply due to overlapping content in the predictors and criteria. Furthermore, the schizotypy dimensional scores identified elevated rates of SWM deficits in participants who were drawn from a nonclinically ascertained sample and who were functioning well enough to attend college (making for a conservative test of the hypotheses—as schizotypes experiencing marked SWM deficits would presumably be disadvantaged for gaining college admission).

Schizotypy and COMT

The finding of the hypothesized allele-dependent relation between Val and negative, but not positive, schizotypy supports the construct validity of a multidimensional model of schizotypy. Moreover, it suggests that COMT contributes to a biological differentiation between the two dimensions and grounds negative schizotypy in molecular genetics. The present findings are consistent with the notion that negative schizotypy serves as a trait-like expression of hypodopaminergic functioning in the prefrontal cortex, whereas positive schizotypy may be due, in part, to hyperdopaminergic functioning (e.g., Davis et al., 1991). Indeed, positive symptoms have been linked to hyperdopaminergic functioning in the striatum (Meyer-Lindenberg et al., 2005).

Although the above statement is undoubtedly an oversimplification of the complex processes underlying the development of positive and negative schizotypy, it does suggest that the etiology underlying the dimensions may be separate, but related disease processes. Conceptualizing and measuring positive and negative schizotypy (and by extension schizophrenia) in this manner may help to clarify mixed findings in literature – which often treats schizophrenia spectrum disorders as discrete and homogenous entities.

Stefanis and colleagues (e.g., (Avramopoulos et al., 2002; Smyrnis et al., 2007; Stefanis et al., 2004) previously examined this association using the Schizotypy Personality Questionnaire, an inventory that assesses schizotypal personality traits based on the diagnostic criteria for the disorder. The results supported an association between Val allele and schizotypal symptoms, particularly negative and disorganized symptoms. The present study broadened these findings to include milder expressions of illness along the negative schizotypy continuum. Given that milder expressions of negative schizotypy have been associated with the development of schizophrenia spectrum disorders (e.g., Kwapil, 1998), it is essential to examine this association across a broad range of schizotypy to improve our ability to identify those at risk. In the present study, the linear relation between COMT (i.e., number of Val alleles) and negative schizotypy accounted for approximately 4% of the variance in negative schizotypy, consistent with Stefanis et al. (2004). This small to medium effect size supports the view that the schizotypy continuum (including schizotypal personality disorder and schizophrenia) arises from multiple genetic and nongenetic factors. Indeed, a number of other genes have been implicated in the development of schizophrenia such as DRD1, DTNBP1, MTHFR, and

TPH1 (Allen et al., 2008). Future studies should examine how assessing multiple single nucleotide polymorphisms or genes within the same functional system may improve our understanding of the genetic underpinnings of positive and negative schizotypy.

The impact of COMT on dopamine metabolism provides a promising mechanism for understanding the link between negative symptoms and hypodopaminergic functioning in the prefrontal cortex. Negative symptoms reflect a diminution of normal functions and scholars dating back to Bleuler (1911/1920) suggested that negative symptoms are the fundamental feature of schizophrenia. A small literature has directly examined how altering prefrontal dopamine availability differentially impacts psychometrically identified positive and negative schizotypy – but no study has examined whether this direct relationship is moderated by COMT genotype. In a study examining whether controlled dopamine administration impacted language functions, Mohr et al. (2005) found increased right hemisphere language contribution was related to increasing positive schizotypy scores in a placebo, but not the levodopa, group. In contrast, better left hemisphere lexical decision performance was associated with increasing negative schizotypy scores in a levodopa group. This suggests that increasing dopamine availability contributes to a positive association between negative schizotypy scores and improvement in performance on basic language functions. In other words, elevated dopamine levels may have a beneficial effect for individuals high on negative schizotypy who are presumed to have low baseline levels of dopamine. These findings are in line with those of the present study in that they support the notion that dopamine availability

differentially impacts positive and negative schizotypy, consistent with a multidimensional model of schizotypy.

Despite its clinical salience, few studies have reported an association between COMT and psychometrically identified positive schizotypy. Only Avramopoulos et al. (2002) found an association between COMT and the Perceptual Aberration Scale; however, the pattern of this finding (i.e., Val homozygotes had the highest scores, followed by Met homozygotes, and then Val/Met heterozygotes) is somewhat counterintuitive. Note that the authors reported a different pattern using the overall score from the Schizotypal Personality Questionnaire in the same study. A questionable relation between COMT and positive schizotypy may be due to the notion that positive symptoms are presumed to result from a transient neurochemical imbalance due to their episodic nature and better response to medication. Moreover, results from brain imaging studies suggest an association between positive symptoms and temporal rather than prefrontal regions of the brain (e.g., Wible et al., 2009). More research is needed to clarify the nature of these relationships – especially given that hyperdopaminergic functioning in presumed to contribute to positive symptoms of schizophrenia (e.g., Davis et al., 1991).

Schizotypy and SWM

Consistent with predictions, SWM deficits were associated with negative schizotypy. These findings support an extant literature documenting the presence of working memory deficits in patients with schizophrenia (e.g., Park & Holzman, 1992; Forbes et al., 2009; Lee & Park, 2005), as well as schizotypic individuals identified by

consanguinity (e.g., Diwadkar et al., 2006), clinical status (e.g., Wood et al., 2003), and psychometric screening inventories (e.g., Tallent & Gooding, 1999). In addition, working memory has been proposed as an endophenotype for schizophrenia (Gur et al., 2007) – a phenotypic expression that is more proximal to the genetic diathesis than the disorder itself (Gottesman & Gould, 2003). The presence of working memory deficits across the schizotypy continuum supports working memory as an endophenotype and the conceptualization of schizophrenia as the most extreme manifestation of illness along the schizotypy continuum.

A key component of working memory is the ability to maintain mental representations active above threshold and under the focus of attention, especially during distractions (e.g., Lee & Park, 2005). The present study found an association between negative schizotypy and increased within and double errors. In this case, negative schizotypy was associated with an impaired ability to hold in memory boxes that did not contain a blue token while continuing to search through boxes either within or between trials. Interestingly, the cross-level interaction between negative schizotypy and within and double errors suggest that individuals high on negative schizotypy made more errors even on the easy trials (although this should be interpreted cautiously given that raw data was used to interpret the cross-level interaction). Working memory deficits are largely controlled by the neural circuitry in the dorsolateral prefrontal cortex, in conjunction with the dopaminergic system and posterior parietal cortex (e.g., Goldman-Rakic et al., 2000; Wager & Smith, 2003). Many scholars (e.g., Weinberger et al., 2001) suggest that working memory deficits contribute to negative symptoms (and thus negative schizotypy)

due to impairment in the dorsolateral prefrontal cortex. The results from the present study also support an association between negative schizotypy and increased mean time to first response and mean token search preparation time. Rather than working memory *per se*, these latency measures likely reflect the processing speed deficits characteristic of negative schizotypy (e.g., O'Leary et al., 2000).

There is a general consensus that positive symptoms are unrelated to working memory impairment in schizophrenia (e.g., O'Leary et al., 2000), presumably due to positive symptoms being episodic in nature and manageable by medication. However, the present study found an unhypothesized relationship between positive schizotypy and increased between errors. Rather than indicating working memory deficits *per se*, this association may reflect the distractibility that is characteristic of individuals along the positive schizotypy continuum. Several studies (e.g., Green & Walker, 1986; Walker & Harvey, 1986) reported that positive symptoms are related to increased vulnerability to distraction. Additionally, Diaz et al. (2011) demonstrated that patients with schizophrenia fail to show significant differences in brain activation when processing emotional versus neutral distractors, suggesting an increased vulnerability to general distraction. Indeed, several studies found increased between errors on the CANTAB SWM task in samples with unmedicated participants with AD/HD compared to samples with medicated participants with AD/HD (e.g., Kempton et al., 1999) or controls (e.g., Goldberg et al., 2005; Rhodes et al., 2005), supporting the idea that the results from the present study reflect distractibility rather than working memory deficits *per se*. Moreover, marked positive symptoms might impair participants' ability to take part in a working memory

task; however, this would likely reflect a more generalized deficit rather than a working memory deficit *per se*. Taken together, the general relation between SWM and negative, but positive schizotypy, supports the multidimensional model of schizotypy and suggests a differential cognitive pattern between the two dimensions.

Note that this is the first study to use the CANTAB SWM task in a sample of psychometrically identified schizotypy. The results are consistent with those found in the patient and relative literature and suggest that the CANTAB SWM task is sensitive enough to detect small effect sizes in a nonclinical sample. However, the statistical techniques commonly used in the literature (i.e., zero-order correlations, *t*-tests, unilevel linear regression) would have likely masked this relationship. Therefore, the present study utilized mixed-modeling and negative binomial regressions to account for the nested and skewed nature of the data. To date, this is the only published study to take this statistical approach with the CANTAB SWM task within the schizotypy and schizophrenia literature. Future studies should consider this approach when analyzing similar data – especially when using nonclinical samples in which one would expect small to medium effect sizes.

Schizotypy, COMT, and SWM

Contrary to hypotheses, there was no relation between COMT and SWM performance. Additionally, COMT genotype generally did not moderate the association between SWM performance and negative schizotypy; however, the COMT X negative schizotypy interaction was related to double errors. Although Smyrnis et al. (2007) reported an allele-dependent relation between negative schizotypy and cognitive

performance, the results are largely uninterpretable due to their use of unstandardized coefficients and their *post-hoc* decision to drop latent factors. Thus, this appears to be the first published study to appropriately assess this relationship.

Due to its role in dopamine metabolism in the prefrontal cortex, a large literature has investigated the moderating role of COMT on prefrontally mediated cognitive processes, including working memory, in both healthy controls and patients with schizophrenia. The literature continues to be inconsistent regarding this relationship. For example, several seminal studies suggest that COMT genotype differentially impacts prefrontally mediated cognitive performance (e.g., Egan et al., 2001; Goldberg et al., 2003), meta-analyses yield conflicting results (e.g., Barnett et al., 2007; Barnett et al., 2008), and more recent work (e.g., Wishart et al., 2011; Wirgenes et al., 2010) supports this relation. These inconsistent findings do not suggest that COMT is unrelated to prefrontally mediated cognitive processes. Rather, they likely suggest that COMT plays a small role in contributing to variation in these relations (e.g., Barnett et al., 2008). Moreover, heterogeneity across samples and tasks likely contributes to mixed findings. Future meta-analyses should investigate the moderating role of sample and task characteristics in studies (e.g., age, sex, symptom presentation, type of task) that assess this relationship.

The present study found a significant relation between double errors and the COMT X negative schizotypy interaction. Contrary to hypotheses, negative schizotypy was unrelated to double errors for individuals with Val/Val or Val/Met genotypes, but negative schizotypy had a significant positive association with double errors for

individuals with the Met/Met genotype. It is difficult to interpret these results because Met homozygosity is fairly consistently associated with better, rather than worse, prefrontally mediated cognitive performance (e.g., Egan et al., 2001; Mattay et al., 2003; Barnett et al., 2010). Moreover, drawing upon Mohr et al. (2005), one might predict increased prefrontal dopamine availability (associated with Met/Met genotype) to provide a cognitive advantage for negative schizotypy (which is presumably associated with prefrontal hypodopaminergic functioning). Rather than suggesting a meaningful relationship, this association may reflect a Type I error. More research is needed to clarify the nature of this relationship in psychometrically identified positive and negative schizotypy to determine whether this result can be replicated.

Recent studies have assessed multiple genes or single-nucleotide polymorphisms within the same functionally related systems. In a sample of healthy children, Barnett et al. (2011) found an interaction between MAOA and COMT such that increased prefrontal catecholamine availability was related to better working memory in males. Specifically, MAOA genotype differentially impacted working memory only in the context of COMT Met homozygosity. The results support the idea that COMT is one source of variation that contributes to working memory processes. Moreover, understanding how COMT interacts with other genes and single-nucleotide polymorphisms will improve our ability to understand the genetic basis of prefrontally mediated cognitive processes. However, even complex genetic pathways require understanding of the neurobiological pathways and environmental contributors to cognitive functioning.

Implications

The relations between COMT and SWM with negative schizotypy support schizotypy as an expression of neurodevelopmental vulnerability for schizophrenia. Moreover, the results corroborate the notion that neural dysmaturation predates the appearance of schizophrenia and can be detected across the schizotypy continuum. The general lack of interaction between COMT and negative schizotypy in the prediction of SWM highlights the importance of assessing multiple genes or single nucleotide polymorphisms in order to better understand the genetic basis of the cognitive processes associated with negative schizotypy.

The differential relation between COMT and SWM and positive and negative schizotypy supports the multidimensional construct of schizotypy. This does not mean, however, that schizotypy is limited to only two factors. Although the positive and negative symptom dimensions are the most widely reported factors of schizotypy and schizophrenia, the focus on and identification of these factors admittedly reflects the nature of the measures administered. Furthermore, although psychometric screening tools providing promising starting points for identifying schizotypy, they undoubtedly lack the sensitivity and specificity for assessing schizotypy that structured interviews possess.

There are two predominant views regarding the underlying nature of schizotypy. Some scholars (e.g., Claridge, 1986) regard schizotypy as being a fully dimensional model of personality. Others (e.g., Meehl, 1962) theorize that schizotypy is taxonic in nature, representing a pathological process of neurodevelopment. Taxometric methods and finite mixture modeling support schizotypy as taxonic in nature (Lenzenweger &

Korfine, 1992; Lenzenweger, McLachlan, & Rubin, 2007). Despite these differing conceptualizations, both viewpoints regard schizotypy as a multidimensional model with increasing expressions of severity along the continuum. The purpose of the present study was not to resolve whether schizotypy is continuous or discontinuous in nature, but rather to further validate the multidimensional construct of schizotypy. However, construct validation of these dimensions should help clairfy this larger issue.

The present study also supports the psychometric methods as a promising tool for detecting variation related to COMT, SWM, and schizotypy. The psychometric method is a promising point of entry but should be used in combination with other domains relevant to multidimensional schizotypy (e.g., genetic, biobehavioral, cognitive, and clinical) to better understand the etiology of schizophrenia. This will provide a basis for longitudinal study, which will further our understanding of multidimensional schizotypy, and contribute to the development of preventative interventions.

REFERENCES

Agresti, A. (2007). An introduction to categorical data analyses – second edition. Hoboken, New Jersey: John Wiley & Sons, Inc.

Allen, N.C., Bagade, S., McQueen, M.B., Ioannidis, J.P.A., Kavvoura, F.K., Khoury, M.J., Tanzi, R.E., & Bertram, L. (2008). Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. Nature Genetics, 40, 827-834.

Andreasen, N. C. (1999). A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. Archives of General Psychiatry, 56(9), 781-787.

Andreasen, N. C., O'Leary, D. S., Cizadlo, T., Arndt, S., Rezai, K., Ponto, L. L., Watkins, G. L., & Hichwa, R. D. (1996). Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. Proceedings of the National Academy of Sciences of the United States of America, 93(18), 9985-9990.

Avramopoulos, D., Stefanis, N. C., Hantoumi, I., Smyrnis, N., Evdokimidis, I., & Stefanis, C. N. (2002). Higher scores of self reported schizotypy in healthy young males carrying the COMT high activity allele. Molecular Psychiatry, 7(7), 706-711.

Badcock, J. C., Michiel, P. T., & Rock, D. (2005). Spatial working memory and planning ability: contrasts between schizophrenia and bipolar I disorder. Cortex, 41(6), 753-763.

Baddeley, A. D. (1986). Working memory. London Oxford University Press.

Barnes, T. R., Mutsatsa, S. H., Hutton, S. B., Watt, H. C., & Joyce, E. M. (2006). Comorbid substance use and age at onset of schizophrenia. British Journal of Psychiatry, 188, 237-242.

Barnett, J.H., Heron, J., Ring, S.M., Golding, J., Goldman, D., Xu, K., & Jones, P.B. (2007). Gender-specific effects of the catechol-O-methyltransferase Val108/158Met polymorphism on cognitive function in children. American Journal of Psychiatry 164,142–149.

Barnett, J.H., Scoriels, L., & Munafò, M.R. (2008). Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. Biological Psychiatry, 64, 137-144.

Barnett, J.H., Xu, K., Heron, J., Goldman, D., & Jones, P.B. (2011). Cognitive effects of genetic variation in monoamine neurotransmitter Systems: A population-based study of COMT, MAOA, and 5HTTLPR. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 156(2), 158-167.

Barrett, S. L., Bell, R., Watson, D., & King, D. J. (2004). Effects of amisulpride, risperidone and chlorpromazine on auditory and visual latent inhibition, prepulse inhibition, executive function and eye movements in healthy volunteers. Journal of Psychopharmacology, 18(2), 156-172.

Bartok, E., Berecz, R., Glaub, T., & Degrell, I. (2005). Cognitive functions in prepsychotic patients. Progress in Neuropsychopharmacology & Biological Psychiatry, 29(4), 621-625.

Bergida, H., & Lenzenweger, M. F. (2006). Schizotypy and sustained attention: confirming evidence from an adult community sample. Journal of Abnormal Psychology, 115(3), 545-551.

Bilder, R. M., Volavka, J., Czobor, P., Malhotra, A. K., Kennedy, J. L., Ni, X., Goldman, R. S., Hoptman, M. J., Sheitman, B., Lindenmayer, J. P., Citrome, L., McEvoy, J. P., Kunz, M., Chakos, M., Cooper, T. B., & Lieberman, J. A. (2002). Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. Biological Psychiatry, 52(7), 701-707.

Bleuler, E.P. (1911/1950). Dementia praecox or the group of schizophrenias. New York, NY: International Universities Press.

Brown, L. H., Silvia, P. J., Myin-Germeys, I., Lewandowski, K. E., & Kwapil, T. R. (2008). The relationship of social anxiety and social anhedonia to psychometrically identified schizotypy. Journal of Social and Clinical Psychology, 27, 127-149.

Callicott, J. H., Bertolino, A., Egan, M. F., Mattay, V. S., Langheim, F. J., & Weinberger, D. R. (2000). Selective relationship between prefrontal N-acetylaspartate measures and negative symptoms in schizophrenia. American Journal of Psychiatry, 157(10), 1646-1651.

Cannon, T. D., van Erp, T. G., Bearden, C. E., Loewy, R., Thompson, P., Toga, A. W., Huttunen, M. O., Keshavan, M. S., Seidman, L. J., & Tsuang, M. T. (2003). Early and late neurodevelopmental influences in the prodrome to schizophrenia:

contributions of genes, environment, and their interactions. Schizophrenia Bulletin, 29(4), 653-669.

Cannon, T. D., Zorrilla, L. E., Shtasel, D., Gur, R. E., Gur, R. C., Marco, E. J., Moberg, P., & Price, R. A. (1994). Neuropsychological functioning in siblings discordant for schizophrenia and healthy volunteers. Archives of General Psychiatry, 51(8), 651-661.

Chapman, J.P., Chapman, L.J., Kwapil, T.R. (1995). Scales for the measurement of schizotypy. In: A.Raine, T.Lencz, and S. Mednick (Eds.) Schizotypal Personality Disorder, Cambridge University Press, Cambridge, England.

Chapman, L. J., & Chapman, J. P. (1983). Infrequency Scale for Personality Measures. Unpublished scale available from T.R. Kwapil. Department of Psychology, University of North Carolina at Greensboro. Greensboro, NC 27402.

Chapman, L. J., Chapman, J. P., Kwapil, T. R., Eckblad, M., & Zinser, M. C. (1994). Putatively psychosis-prone subjects 10 years later. Journal of Abnormal Psychology, 103(2), 171-183.

Chapman, L. J., Chapman, J. P., & Raulin, M. L. (1976). Scales for physical and social anhedonia. Journal of Abnormal Psychology, 85(4), 374-382.

Chapman, L. J., Chapman, J. P., & Raulin, M. L. (1978). Body-image aberration in Schizophrenia. Journal of Abnormal Psychology, 87(4), 399-407.

Chen, J., Lipska, B. K., Halim, N., Ma, Q. D., Matsumoto, M., Melhem, S., Kolachana, B. S., Hyde, T. M., Herman, M. M., Apud, J., Egan, M. F., Kleinman, J. E., & Weinberger, D. R. (2004). Functional analysis of genetic variation in catechol-O-

methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. American Journal of Human Genetics, 75(5), 807-821.

Chok, J. T., Kwapil, T. R., & Scheuermann, A. (2005). Dermatoglyphic anomalies in psychometrically identified schizotypic young adults. Schizophrenia Research, 72(2-3), 205-214.

Claridge, G., McCreery, C., Mason, O., Bentall, R., Boyle, G., Slade, P., & Popplewell, D. (1996). The factor structure of "schizotypal' traits: a large replication study. British Journal of Clinical Psychology, 35 (Pt 1), 103-115.

Claridge, G. S., & Broks, P. (1984). Schizotypy and hemisphere function: Theoretical considerations and the measurement of schizotypy. Personality and Individual Differences, 5, 633-648.

Cocchi, L., Walterfang, M., Testa, R., Wood, S. J., Seal, M. L., Suckling, J., Takahashi, T., Proffitt, T. M., Brewer, W. J., Adamson, C., Soulsby, B., Velakoulis, D., McGorry, P. D., & Pantelis, C. (2009). Grey and white matter abnormalities are associated with impaired spatial working memory ability in first-episode schizophrenia. Schizophrenia Research, 115(2-3), 163-172.

Cohen, J., Cohen, P., West, S.G., & Aiken, L.S. (2003). Applied multiple regression/correlation analysis for the behavioral sciences – third edition. Mahwah, New Jersey: Lawrence Erlbaum Associates, Inc.

Conklin, H. M., Curtis, C. E., Katsanis, J., & Iacono, W. G. (2000). Verbal working

memory impairment in schizophrenia patients and their first-degree relatives: evidence from the digit span task. American Journal of Psychiatry, 157(2), 275-277.

Cornblatt, B. A., Lenzenweger, M. F., & Erlenmeyer-Kimling, L. (1989). The continuous performance test, identical pairs version: II. Contrasting attentional profiles in schizophrenic and depressed patients. Psychiatry Research, 29(1), 65-85.

Cornblatt, B. A., Risch, N. J., Faris, G., Friedman, D., & Erlenmeyer-Kimling, L. (1988). The Continuous Performance Test, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families. Psychiatry Research, 26(2), 223-238.

Daniels, J. K., Williams, N. M., Williams, J., Jones, L. A., Cardno, A. G., Murphy, K. C., Spurlock, G., Riley, B., Scambler, P., Asherson, P., McGuffin, P., & Owen, M. J. (1996). No evidence for allelic association between schizophrenia and a polymorphism determining high or low catechol O-methyltransferase activity. American Journal of Psychiatry, 153(2), 268-270.

Davis, K.L., Kahn, R.S., Ko, G., & Davidson, M. (1991). Dopamine in schizophrenia: a review and reconceptualization. American Journal of Psychiatry 148, 1474-1486.

Derogatis, R. (1993). Symptom Checklist-90-R (SCL-90-R). Minneapolis: Computer Systems.

Diaz, M.T., He, G., Gadde, S., Bellion, C., Belger, A., Voyvodic, J.T., McCarthy, G. (in

press). The influence of emotional distration on verbal working memory: An fMRI investigation comparing individuals with schizophrenia and healthy adults. Journal of Psychiatric Research.

Diwadkar, V. A., Montrose, D. M., Dworakowski, D., Sweeney, J. A., & Keshavan, M. S. (2006). Genetically predisposed offspring with schizotypal features: an ultra high-risk group for schizophrenia? Progress in Neuropsychopharmacology & Biological Psychiatry, 30(2), 230-238.

Docherty, A. R., & Sponheim, S. R. (2008). Anhedonia as a phenotype for the Val158Met COMT polymorphism in relatives of patients with schizophrenia. Journal of Abnormal Psychology, 117(4), 788-798.

Eckblad, M., & Chapman, L. J. (1983). Magical ideation as an indicator of schizotypy. Journal of Consulting and Clinical Psychology, 51(2), 215-225.

Eckblad, M., Chapman, L. J., Chapman, J. P., & Mishlove, M. (1982). The Revised Social Anhedonia Scale. Unpublished test copies available from T.R. Kwapil.

Department of Psychology, University of North Carolina at Greensboro. Greensboro, NC.

Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., Goldman, D., & Weinberger, D. R. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proceedings of the National Academy of Sciences of the United States of America, 98(12), 6917-6922.

Elliot, R., McKenna, P. J., Robbins, T. W., & Sahakian, B. I. (1998). Specific

neuropsychological deficits in schizophrenic patients with preserved intellectual function. Cognitive Neuropsychiatry, 3, 45-70.

Engle, R. W., & Kane, M. J. (2004). Executive attention, working memory capacity, and a two-factor theory of cognitive control. New York: Academic Press.

Erlenmeyer-Kimling, L., Cornblatt, B. A., Rock, D., Roberts, S., Bell, M., & West, A. (1993). The New York High-Risk Project: anhedonia, attentional deviance, and psychopathology. Schizophrenia Bulletin, 19(1), 141-153.

Ettinger, U., Joober, R., R, D. E. G., & O'Driscoll G, A. (2006). Schizotypy, attention deficit hyperactivity disorder, and dopamine genes. Psychiatry and Clinical Neurosciences, 60(6), 764-767.

Fatemi, S.H. & Folsom, T.D. (2009). The neurodevelopmental hypothesis of schizophrenia, revisted. Schizophrenia Bulletin, 35(3), 528-548.

Fan, J. B., Zhang, C. S., Gu, N. F., Li, X. W., Sun, W. W., Wang, H. Y., Feng, G. Y., St Clair, D., & He, L. (2005). Catechol-O-methyltransferase gene Val/Met functional polymorphism and risk of schizophrenia: a large-scale association study plus meta-analysis. Biological Psychiatry, 57(2), 139-144.

Fidell, L.S., & Tabachnick, B.G. (2003). Preparatory Data Analysis. In: J.A. Schinker and W.F. Velicer, Handbook of Psychology: Volume 2, Research Methods in Psychology. John Wiley & Sons: Hoboken, NJ.

Forbes, N. F., Carrick, L. A., McIntosh, A. M., & Lawrie, S. M. (2009). Working memory in schizophrenia: a meta-analysis. Psychological Medicine, 39(6), 889-905.

Gabrovska-Johnson, V. S., Scott, M., Jeffries, S., Thacker, N., Baldwin, R. C., Burns, A., Lewis, S. W., & Deakin, J. F. (2003). Right-hemisphere encephalopathy in elderly subjects with schizophrenia: evidence from neuropsychological and brain imaging studies. Psychopharmacology (Berl), 169(3-4), 367-375.

Gallinat, J., Bajbouj, M., Sander, T., Schlattmann, P., Xu, K., Ferro, E. F., Goldman, D., & Winterer, G. (2003). Association of the G1947A COMT (Val(108/158)Met) gene polymorphism with prefrontal P300 during information processing. Biological Psychiatry, 54(1), 40-48.

Gevins, A., Smith, M. E., Le, J., Leong, H., Bennett, J., Martin, N., McEvoy, L., Du, R., & Whitfield, S. (1996). High resolution evoked potential imaging of the cortical dynamics of human working memory. Electroencephalography and Clinical Neurophysiology, 98(4), 327-348.

Geyer, M. A. (2008). Developing translational animal models for symptoms of schizophrenia or bipolar mania. Neurotoxicity Research, 14(1), 71-78.

Glatt, S. J., Faraone, S. V., & Tsuang, M. T. (2003). Association between a functional catechol O-methyltransferase gene polymorphism and schizophrenia: meta-analysis of case-control and family-based studies. American Journal of Psychiatry, 160(3), 469-476.

Goghari, V. M., & Sponheim, S. R. (2008). Differential association of the COMT Val158Met polymorphism with clinical phenotypes in schizophrenia and bipolar disorder. Schizophrenia Research, 103(1-3), 186-191.

Gogos, J. A., Morgan, M., Luine, V., Santha, M., Ogawa, S., Pfaff, D., & Karayiorgou,

M. (1998). Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. Proceedings of the National Academy of Sciences of the United States of America, 95(17), 9991-9996.

Gold, J. M., Carpenter, C., Randolph, C., Goldberg, T. E., & Weinberger, D. R. (1997). Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. Archives of General Psychiatry, 54(2), 159-165.

Goldberg, T. E., Egan, M. F., Gscheidle, T., Coppola, R., Weickert, T., Kolachana, B. S., Goldman, D., & Weinberger, D. R. (2003). Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. Archives of General Psychiatry, 60(9), 889-896.

Goldberg, M.C., Mostofsky, S.H., Cutting, L.E., Majone, E.M., Astor, B.C., Denckla, M.B., & Landa, R.J. (2005). Subtle executive impairment in chilren with autism and children with ADHD. Journal of Autism and Developmental Disorders, 35(3), 279-293.

Goldman-Rakic, P. S. (1994). Working memory dysfunction in schizophrenia. Journal of Neuropsychiatry and Clinical Neurosciences, 6(4), 348-357.

Goldman-Rakic, P. S., Muly, E. C., 3rd, & Williams, G. V. (2000). D(1) receptors in prefrontal cells and circuits. Brain Research Reviews, 31(2-3), 295-301.

Goldman-Rakic, P. S., & Selemon, L. D. (1997). Functional and anatomical aspects of prefrontal pathology in schizophrenia. Schizophrenia Bulletin, 23(3), 437-458.

Gottesman, I.I. & Gould, T.D. (2003). The endophenotype concept in psychiatry:

etymology and strategic intentions. American Journal of Psychiatry, 160, 636–645.

Green, M. & Walker, E. (1986). Attentional performance in positive and negative symptom schizophrenia. The Journal of Nervous and Mental Disease, 74(4):208-13.

Gur, R.E., Calkins, M.E., Gur, R.C., Horan, W.P., Nuechterlein, K.H., Seidman, L.J., & Stone, W.S. (2007). The consortium on the genetics of schizophrenia: neurocognitive endophenotypes. Schizophrenia Bulletin, 33(1), 49-68.

Han, D. H., Kee, B. S., Min, K. J., Lee, Y. S., Na, C., Park, D. B., & Lyoo, I. K. (2006). Effects of catechol-O-methyltransferase Val158Met polymorphism on the cognitive stability and aggression in the first-onset schizophrenic patients. Neuroreport, 17(1), 95-99.

Harris, M. E. (1988). Wisconsin Card Sorting Test: Scoring Program (Version 2.0). Odessa: Psychological Assessment Resources.

Horan, W. P., Blanchard, J. J., Gangestad, S. W., & Kwapil, T. R. (2004). The psychometric detection of schizotypy: do putative schizotypy indicators identify the same latent class? Journal of Abnormal Psychology, 113(3), 339-357.

Hox, J. (2002). Multilevel analysis: Techniques and applications. Mahwah, NJ: Erlbaum Associates.

Hutton, S. B., Huddy, V., Barnes, T. R., Robbins, T. W., Crawford, T. J., Kennard, C., &

Joyce, E. M. (2004). The relationship between antisaccades, smooth pursuit, and executive dysfunction in first-episode schizophrenia. Biological Psychiatry, 56(8), 553-559.

Hutton, S. B., Puri, B. K., Duncan, L. J., Robbins, T. W., Barnes, T. R., & Joyce, E. M. (1998). Executive function in first-episode schizophrenia. Psychological Medicine, 28(2), 463-473.

Jarskog, L. F., Gilmore, J. H., & Lieberman, J. A. (2004). Neurodegenerative models of schizophrenia. New York: Cambridge University Press.

Johnson, J. K., Tuulio-Henriksson, A., Pirkola, T., Huttunen, M. O., Lonnqvist, J., Kaprio, J., & Cannon, T. D. (2003). Do schizotypal symptoms mediate the relationship between genetic risk for schizophrenia and impaired neuropsychological performance in co-twins of schizophrenic patients? Biological Psychiatry, 54(11), 1200-1204.

Joyce, E., Hutton, S., Mutsatsa, S., Gibbins, H., Webb, E., Paul, S., Robbins, T., & Barnes, T. (2002). Executive dysfunction in first-episode schizophrenia and relationship to duration of untreated psychosis: the West London Study. British Journal of Psychiatry Supplement, 43, s38-44.

Joyce, E. M., Hutton, S. B., Mutsatsa, S. H., & Barnes, T. R. (2005). Cognitive heterogeneity in first-episode schizophrenia. British Journal of Psychiatry, 187, 516-522.

Kaczorowski, J.A., Salinger, W.L., Henrich, V.C., Lewandowski, K.E., Barrantes-Vidal,

N., Kwapil, T.R. (revise and resubmit). Gene affecting dopamine metabolism underlies schizophrenia risk in young adults.

Kaczorowski, J. A., Barrantes-Vidal, N., & Kwapil, T. R. (2009). Neurological soft signs in psychometrically identified schizotypy. Schizophrenia Research, 115(2-3), 293-302.

Kempton, S., Vance, A., Maruff, P., Luk, E., Costin, J., & Pantelis, C. (1999). Executive function and attention deficit hyperactivity disorder: stimulant medication and better executive function performance in children. Psychological Medicine, 29(3), 527-528.

Kerns, J. G., & Becker, T. M. (2008). Communication disturbances, working memory, and emotion in people with elevated disorganized schizotypy. Schizophrenia Research, 100(1-3), 172-180.

Kremer, I., Pinto, M., Murad, I., Muhaheed, M., Bannoura, I., Muller, D. J., Schulze, T. G., Reshef, A., Blanaru, M., Gathas, S., Goichman, R., Rietschel, M., Dobrusin, M., Bachner-Melman, R., Nemanov, L., Belmaker, R. H., Maier, W., & Ebstein, R. P. (2003). Family-based and case-control study of catechol-O-methyltransferase in schizophrenia among Palestinian Arabs. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 119B(1), 35-39.

Kunugi, H., Vallada, H. P., Sham, P. C., Hoda, F., Arranz, M. J., Li, T., Nanko, S., Murray, R. M., McGuffin, P., Owen, M., Gill, M., & Collier, D. A. (1997). Catechol-O-methyltransferase polymorphisms and schizophrenia: a transmission

disequilibrium study in multiply affected families. Psychiatric Genetics, 7(3), 97-101.

Kwapil, T. R. (1998). Social anhedonia as a predictor of the development of schizophrenia-spectrum disorders. Journal of Abnormal Psychology, 107(4), 558-565.

Kwapil, T. R., Barrantes-Vidal, N., & Silvia, P. J. (2008). The dimensional structure of the Wisconsin Schizotypy Scales: factor identification and construct validity. Schizophrenia Bulletin, 34(3), 444-457.

Kwapil, T.R., Chapman, L.J., & Chapman, J. (1999). Validity and usefulness of the Wisconsin Manual for rating psychotic-like experiences. Schizophrenia Bulletin, 25, 363-375.

Lachman, H. M., Nolan, K. A., Mohr, P., Saito, T., & Volavka, J. (1998). Association between catechol O-methyltransferase genotype and violence in schizophrenia and schizoaffective disorder. American Journal of Psychiatry, 155(6), 835-837.

Lachman, H. M., Papolos, D. F., Saito, T., Yu, Y. M., Szumlanski, C. L., & Weinshilboum, R. M. (1996). Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics, 6(3), 243-250.

Lee, J., & Park, S. (2005). Working memory impairments in schizophrenia: a meta-analysis. Journal of Abnormal Psychology, 114(4), 599-611.

Lenzenweger, M. F., & Gold, J. M. (2000). Auditory working memory and verbal recall memory in schizotypy. Schizophrenia Research, 42(2), 101-110.

Lenzenweger, M. F., & Korfine, L. (1992). Confirming the latent structure and base rate of schizotypy: a taxometric analysis. Journal of Abnormal Psychology, 101(3), 567-571.

Lenzenweger, M.F., McLachlan, G., & Rubin, D.B (2007). Resolving the latent structure of schizophrenia endophenotypes using expectation-maximization-based finite mixture modeling. Journal of Abnormal Psychology, 116(1), 16-29.

Lewandowski, K. E., Barrantes-Vidal, N., Nelson-Gray, R. O., Clancy, C., Kepley, H. O., & Kwapil, T. R. (2006). Anxiety and depression symptoms in psychometrically identified schizotypy. Schizophrenia Research, 83(2-3), 225-235.

Lewis, D. A., Melchitzky, D. S., Sesack, S. R., Whitehead, R. E., Auh, S., & Sampson, A. (2001). Dopamine transporter immunoreactivity in monkey cerebral cortex: regional, laminar, and ultrastructural localization. Journal of Comparative Neurology, 432(1), 119-136.

Liao, S.Y., Lin, S.H., Liu, C.M., Hsieh, M.H., Hwang, T.J., Liu, S.K., Guo, S.C., Hwu, H.G. & Chen, W.J. (2009). Genetic variants in COMT and neurocognitive impairment in families of patients with schizophrenia. Genes, Brain, and Behavior, 8, 28-237.

Lotta, T., Vidgren, J., Tilgmann, C., Ulmanen, I., Melen, K., Julkunen, I., & Taskinen, J. (1995). Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme. Biochemistry, 34(13), 4202-4210.

Luke, D.A. (2004). Multilevel modeling. Thousand Oaks, CA: Sage.

Ma, X., Sun, J., Yao, J., Wang, Q., Hu, X., Deng, W., Sun, X., Liu, X., Murray, R. M., Collier, D. A., & Li, T. (2007). A quantitative association study between schizotypal traits and COMT, PRODH and BDNF genes in a healthy Chinese population. Psychiatry Research, 153(1), 7-15.

Matheson, S., & Langdon, R. (2008). Schizotypal traits impact upon executive working memory and aspects of IQ. Psychiatry Research, 159(1-2), 207-214.

Mattay, V. S., Goldberg, T. E., Fera, F., Hariri, A. R., Tessitore, A., Egan, M. F., Kolachana, B., Callicott, J. H., & Weinberger, D. R. (2003). Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. Proceedings of the National Academy of Sciences of the United States of America, 100(10), 6186-6191.

McCartan, D., Bell, R., Green, J. F., Campbell, C., Trimble, K., Pickering, A., & King, D. J. (2001). The differential effects of chlorpromazine and haloperidol on latent inhibition in healthy volunteers. Journal of Psychopharmacology, 15(2), 96-104.

McGuffin, P., Tandon, K., & Corsico, A. (2003). Linkage and association studies of schizophrenia. Current Psychiatry Reports, 5(2), 121-127.

Meehl, P.E. (1962). Schizotaxia, schizotypy, schizophrenia. American Psychologist, 17, 827- 828.

Meehl, P. E. (1990). Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. . Journal of Personality Disorders, 4, 1-99.

Meyer-Lindenberg, A., Kohn, P. D., Kolachana, B., Kippenhan, S., McInerney-Leo, A.,

Nussbaum, R., Weinberger, D. R., & Berman, K. F. (2005). Midbrain dopamine and prefrontal function in humans: interaction and modulation by COMT genotype. Nature Neuroscience, 8(5), 594-596.

Miers, T. C., & Raulin, M. L. (1987). Cognitive slippage scale. New York: Free Press.

Mohr, C., Krummenacher, P., Landis, T., Sandor, P.S., Fathi, M., & Brugger, P. (2005). Psychometric schizotypy modulates levodopa effects on lateralized lexical decision performance. Journal of Psychiatric Research, 39, 241-250.

Molero, P., Ortuno, F., Zalacain, M., & Patino-Garcia, A. (2007). Clinical involvement of catechol-O-methyltransferase polymorphisms in schizophrenia spectrum disorders: influence on the severity of psychotic symptoms and on the response to neuroleptic treatment. Pharmacogenomics Journal, 7(6), 418-426.

Myles-Worsley, M., & Park, S. (2002). Spatial working memory deficits in schizophrenia patients and their first degree relatives from Palau, Micronesia. American Journal of Medical Genetics, 114(6), 609-615.

Noguchi, H., Hori, H., & Kunugi, H. (2008). Schizotypal traits and cognitive function in healthy adults. Psychiatry Research, 161(2), 162-169.

Nolan, K. A., Volavka, J., Czobor, P., Cseh, A., Lachman, H., Saito, T., Tiihonen, J., Putkonen, A., Hallikainen, T., Kotilainen, I., Rasanen, P., Isohanni, M., Jarvelin, M. R., & Karvonen, M. K. (2000). Suicidal behavior in patients with schizophrenia is related to COMT polymorphism. Psychiatric Genetics, 10(3), 117-124.

O'Connor, M., Harris, J.M., McIntosh, A.M., Owens, D.G., Lawrie, S.M., Johnstone,

E.C. (2009). Specific cognitive deficits in a group of genetic high risk schizophrenia. Psychological Medicine, 39(10), 1649-1655.

Okochi, T., Ikeda, M., Kishi, T., Kawashima, K., Kinoshita, Y., Kitajima, T., Yamanouchi, Y., Tomita, M., Inada, T., Ozaki, N., & Iwata, N. (2009). Meta-analysis of association between genetic variants in COMT and schizophrenia: an update. Schizophrenia Research, 110(1-3), 140-148.

O'Leary, D.S., Flaum, M., Kesler, M.L., Flashman, L.A., Arnt, S., & Andreasen, N.C. (2000). Cognitive correlates of the negative, disorganized, and psychotic symtom dimensions of schizphrenia. Journal of Neuropsychiatry and Clinical Neuroscience, 12(1), 4-15.

Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. Neuropsychologia, 28(10), 1021-1034.

Owen, A. M., Doyon, J., Petrides, M., & Evans, A. C. (1996). Planning and spatial working memory: a positron emission tomography study in humans. European Journal of Neuroscience, 8(2), 353-364.

Owen, A. M., Evans, A. C., & Petrides, M. (1996). Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. Cerebral Cortex, 6(1), 31-38.

Owen, M. J., Williams, N. M., & O'Donovan, M. C. (2004). The molecular genetics of schizophrenia: new findings promise new insights. Molecular Psychiatry, 9(1), 14-27.

Pantelis, C., Barnes, T. R., Nelson, H. E., Tanner, S., Weatherley, L., Owen, A. M., & Robbins, T. W. (1997). Frontal-striatal cognitive deficits in patients with chronic schizophrenia. Brain, 120 (Pt 10), 1823-1843.

Pantelis, C., Harvey, C. A., Plant, G., Fossey, E., Maruff, P., Stuart, G. W., Brewer, W. J., Nelson, H. E., Robbins, T. W., & Barnes, T. R. (2004). Relationship of behavioural and symptomatic syndromes in schizophrenia to spatial working memory and attentional set-shifting ability. Psychological Medicine, 34(4), 693-703.

Pantelis, C., Stuart, G. W., Nelson, H. E., Robbins, T. W., & Barnes, T. R. (2001). Spatial working memory deficits in schizophrenia: relationship with tardive dyskinesia and negative symptoms. American Journal of Psychiatry, 158(8), 1276-1285.

Pantelis, C., Wood, S. J., Proffitt, T. M., Testa, R., Mahony, K., Brewer, W. J., Buchanan, J. A., Velakoulis, D., & McGorry, P. D. (2009). Attentional set-shifting ability in first-episode and established schizophrenia: Relationship to working memory. Schizophrenia Research, 112(1-3), 104-113.

Park, S., & Holzman, P. S. (1992). Schizophrenics show spatial working memory deficits. Archives of General Psychiatry, 49(12), 975-982.

Park, S., Holzman, P. S., & Goldman-Rakic, P. S. (1995). Spatial working memory deficits in the relatives of schizophrenic patients. Archives of General Psychiatry, 52(10), 821-828.

Park, S., Holzman, P. S., & Lenzenweger, M. F. (1995). Individual differences in spatial

working memory in relation to schizotypy. Journal of Abnormal Psychology, 104(2), 355-363.

Park, S., & McTigue, K. (1997). Working memory and the syndromes of schizotypal personality. Schizophrenia Research, 26(2-3), 213-220.

Rapoport J.L., Addington, A.M., Frangou, S., & Psych, M.R. (2005). The neurodevelopmental model of schizophrenia: update 2005. Molecular Psychiatry 10, 434-449

Raine, A. (1991). The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophrenia Bulletin, 17(4), 555-564.

Raven, J. C. (1982). Revised Manual for Raven's Progressive Matrices and Vocabulary Scales. Windsor: NFER-Nelson.

Rust, J. (1989). Rust Inventory of Schizotypal Cognitions Manual. . Sidcup, Kent: Psychological Corporation.

Rhodes, S.M., Coghill, D.R., Matthews, L. (2005). Neuropsychological funcitoning in stimulant-naïve boys with hyperkinetic disorder. Psychological Medicine, 35(8), 1109-1120.

Sazci, A., Ergul, E., Kucukali, I., Kilic, G., Kaya, G., & Kara, I. (2004). Catechol-O-methyltransferase gene Val108/158Met polymorphism, and susceptibility to schizophrenia: association is more significant in women. Brain Reseach Molecular Brain Research, 132(1), 51-56.

Schurhoff, F., Szoke, A., Chevalier, F., Roy, I., Meary, A., Bellivier, F., Giros, B., &

Leboyer, M. (2007). Schizotypal dimensions: an intermediate phenotype associated with the COMT high activity allele. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 144B(1), 64-68.

Sheldrick, A. J., Krug, A., Markov, V., Leube, D., Michel, T. M., Zerres, K., Eggermann, T., & Kircher, T. (2008). Effect of COMT val158met genotype on cognition and personality. Eur Psychiatry, 23(6), 385-389.

Shifman, S., Bronstein, M., Sternfeld, M., Pisante-Shalom, A., Lev-Lehman, E., Weizman, A., Reznik, I., Spivak, B., Grisaru, N., Karp, L., Schiffer, R., Kotler, M., Strous, R. D., Swartz-Vanetik, M., Knobler, H. Y., Shinar, E., Beckmann, J. S., Yakir, B., Risch, N., Zak, N. B., & Darvasi, A. (2002). A highly significant association between a COMT haplotype and schizophrenia. American Journal of Human Genetics, 71(6), 1296-1302.

Smyrnis, N., Avramopoulos, D., Evdokimidis, I., Stefanis, C. N., Tsekou, H., & Stefanis, N. C. (2007). Effect of schizotypy on cognitive performance and its tuning by COMT val158 met genotype variations in a large population of young men. Biological Psychiatry, 61(7), 845-853.

Steganis, N.C., Smyrnis, N., Avramopoulos, D., Evdokimidis, I., Ntzoufras, I., & Stefanis, C.N. (2004). Factorial composition of self-rated schizotypal traits among young males undergoing military training, Schizophrenia Bulletin, 30, 335-350.

Stefanis, N. C., Van Os, J., Avramopoulos, D., Smyrnis, N., Evdokimidis, I., Hantoumi,

I., & Stefanis, C. N. (2004). Variation in catechol-o-methyltransferase val158 met genotype associated with schizotypy but not cognition: a population study in 543 young men. Biological Psychiatry, 56(7), 510-515.

Strous, R. D., Lapidus, R., Viglin, D., Kotler, M., & Lachman, H. M. (2006). Analysis of an association between the COMT polymorphism and clinical symptomatology in schizophrenia. Neurosci Lett, 393(2-3), 170-173.

Strous, R. D., Nolan, K. A., Lapidus, R., Diaz, L., Saito, T., & Lachman, H. M. (2003). Aggressive behavior in schizophrenia is associated with the low enzyme activity COMT polymorphism: a replication study. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 120B(1), 29-34.

Tallent, K. A., & Gooding, D. C. (1999). Working memory and Wisconsin Card Sorting Test performance in schizotypic individuals: a replication and extension. Psychiatry Research, 89(3), 161-170.

Tenhunen, J., Salminen, M., Jalanko, A., Ukkonen, S., & Ulmanen, I. (1993). Structure of the rat catechol-O-methyltransferase gene: separate promoters are used to produce mRNAs for soluble and membrane-bound forms of the enzyme. DNA Cell Biol, 12(3), 253-263.

Tunbridge, E. M., Bannerman, D. M., Sharp, T., & Harrison, P. J. (2004). Catechol-o-methyltransferase inhibition improves set-shifting performance and elevates stimulated dopamine release in the rat prefrontal cortex. J Neurosci, 24(23), 5331-5335.

Tunbridge, E. M., Harrison, P. J., & Weinberger, D. R. (2006). Catechol-o-

methyltransferase, cognition, and psychosis: Val158Met and beyond. Biological Psychiatry, 60(2), 141-151.

Tyson, P. J., Laws, K. R., Roberts, K. H., & Mortimer, A. M. (2005). A longitudinal analysis of memory in patients with schizophrenia. J Clin Exp Neuropsychol, 27(6), 718-734.

Vollema, M. G., & van den Bosch, R. J. (1995). The multidimensionality of schizotypy. Schizophrenia Bulletin, 21(1), 19-31.

Wager, T.D. & Smith, E.E. (2003). Neuroimaging studies of working memory: a meta-analysis. Cognitive, Affective, & Behavioral Neuroscience, 3, 255–274.

Walker, E. & Harvey, P. (1986). Positive and negative symptoms in schizophrenia: attentional performance correlates. Psychopathology, 19, 294-302.

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

Wang, Y., Fang, Y., Shen, Y., & Xu, Q. (2010). Analysis of association between the catechol-O-methyl transferase (COMT) gene and negative symptoms in chronic schizophrenia. Psychiatry Research, 179, 147-150.

Wechsler, D. (1997). WAIS-III. Administration and Scoring Manual. San Antonio: Harcourt Brace & Co.

Weinberger, D. R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. Archives of General Psychiatry, 44(7), 660-669.

Weinberger, D. R., Egan, M. F., Bertolino, A., Callicott, J. H., Mattay, V. S., Lipska, B.

K., Berman, K. F., & Goldberg, T. E. (2001). Prefrontal neurons and the genetics of schizophrenia. Biological Psychiatry, 50(11), 825-844.

Wible, C.G., Lee, K., Molina, I., Hashimoto, R., Preus, A.P., Roach, B.J., Ford, J.M., Mathalon, D.H., McCarthey, G., Turner, J.A., Potkin, S.G., O'Leary, D., Belger, A., Diaz, M., Voyvodic, J., Brown, G.G., Notestine, R., Greve, D., Lauriello, J., & FBIRN. fMRI activity correlated with auditory hallucinations during performance of a working memory task: data from the FBIRN consortium study. Schizophrenia Bulletin, 35, 47-57.

Wirgenes, K.V., Sundet, K., Agartz, I., Athanasiu, L., Mattingsdal, M., Athanasiu, L., Melle, I., & Andreassen, O.A. (2010). Cathecol O-methyltransferase variants and cognitive performance in schizophrenia nd biploar disorder versus controls. Schizophrenia Research, 122(1-3), 31-37.

Wishart, H.A., Roth, R.M., Saykin, A.J., Rhodes, C.H., Tsongalis, G.J., Pattin, K.A., Moore, J.H. & McAllister, T.W. (2011). Journal of the International Neuropsychological Society, 17(1), 174-180.

Wood, S. J., Pantelis, C., Proffitt, T., Phillips, L. J., Stuart, G. W., Buchanan, J. A., Mahony, K., Brewer, W., Smith, D. J., & McGorry, P. D. (2003). Spatial working memory ability is a marker of risk-for-psychosis. Psychological Medicine, 33(7), 1239-1247.

APPENDIX A:

TABLES AND FIGURES

Table 1
Descriptive Statistics

	N	Min	Max	Mean	SD	Skew	Kurtosis
Positive Schizotypy	369	-1.56	3.25	-.27	.86	1.20	1.56
Negative Schizotypy	369	-1.70	4.02	-.03	.95	.76	.68
Positive Schizotypy (transformed)	369	.00	.76	.33	.15	.30	-.31
Negative Schizotypy (transformed)	369	.00	.83	.40	.15	-.14	-.38
COMT	312	0	2	1.09	.732	-.136	-1.121
Between Errors Total	369	0	93	19.77	15.14	1.12	1.60
Between Errors - 4 blocks	369	0	11	.53	1.41	3.81	17.75
Between Errors - 6 blocks	369	0	29	4.82	5.42	1.41	1.90
Between Errors - 8 blocks	369	0	53	14.41	10.76	.73	.036
Within Errors Total	369	0	17	.79	1.84	4.41	26.87
Within Errors - 4 blocks	369	0	9	.08	.63	10.57	129.42
Within Errors - 6 blocks	369	0	5	.16	.62	4.72	24.77
Within Errors - 8 blocks	369	0	16	.55	1.51	5.85	47.85
Double Errors Total	369	0	13	.44	1.23	5.41	39.83
Double Errors - 4 blocks	369	0	3	.02	.21	10.60	126.17
Double Errors - 6 blocks	369	0	4	.07	.35	6.89	58.58
Double Errors - 8 blocks	369	0	13	.35	1.10	6.40	57.45
Mean Time to First Response – 4	369	.55	4.61	1.28	.60	2.71	9.48

Mean Time to First Response - 6	369	.51	4.16	1.36	.53	1.73	4.27
Mean Time to First Response - 8	369	.58	6.03	1.52	.64	2.08	7.88
Mean Time to Last Response - 4	369	8.85	25.18	12.33	2.05	1.64	5.11
Mean Time to Last Response - 6	369	13.98	33.74	20.47	3.91	.89	.56
Mean Time to Last Response - 8	369	20.07	77.32	32.44	7.31	1.57	5.25
Mean Search Preparation Time - 4	369	.49	2.23	.89	.25	1.47	3.19
Mean Search Preparation Time - 6	369	.48	2.55	.90	.27	1.53	4.72
Mean Search Preparation Time - 8	369	.47	2.86	.93	.31	1.89	6.25
Strategy	369	18	47	30.75	5.92	-.32	-.57

Table 2

Spearman Correlations

	Positive Schizotypy (n=369)	**Negative Schizotypy (n=369)**	**COMT[1] (n=311)**
Between Errors Total	.084	-.009	-.053
Between Errors - 4 blocks	.06	-.009	-.075
Between Errors - 6 blocks	.076	.030	-.013
Between Errors - 8 blocks	.064	-.019	-.058
Within Errors Total	.008	.066	.038
Within Errors - 4 blocks	.066	.137**	.059
Within Errors - 6 blocks	-.021	.060	-.006
Within Errors - 8 blocks	.018	.025	.059
Double Errors Total	.013	.063	.059
Double Errors - 4 blocks	.056	.075	.019
Double Errors - 6 blocks	-.03	.086+	.037
Double Errors - 8 blocks	.020	.023	.058
Mean Time to First Response – 4	-.004	-.071	.073
Mean Time to First Response - 6	.031	.106*	.058
Mean Time to First Response - 8	.054	.102*	.030
Mean Time to Last Response - 4	.011	.072	.039
Mean Time to Last Response - 6	.041	.102*	.033
Mean Time to Last Response - 8	.057	.076	.022
Mean Search Preparation Time - 4	-.005	.060	.038
Mean Search Preparation Time - 6	.038	.119*	.070
Mean Search Preparation Time - 8	.055	.124*	.063

Strategy	.123*	.025	.016
Positive Schizotypy		.22***	-.022
Negative Schizotypy			.195***

***p<.001 **p<.01 *$p \leq .05$ +$p < .10$

[1]Note the correlations between positive and negative schizotypy and COMT contained 312 participants.

Table 3

Direct Effects of Positive and Negative Schizotypy with SWM Performance (N = 369)

	Level 2 Predictors	
SWM Level 1 Criterion	Step 1: Positive Schizotypy	Step 1: Negative Schizotypy
Between Errors	**0.892(*SE*=0.370)***	-0.356(*SE*=0.376)
Within Errors	0.400(*SE*=1.119)	**2.578(*SE*=1.024)***
Double Errors	0.852(*SE*=1.188)	**2.871(*SE*=1.069) ****
Time to First Response	0.091(*SE*=0.176)	**0.380(*SE*=0.202) +**
Time to Last Response	1.230(SE=1.221)	2.189(SE=1.372)
Preparation time	0.026(*SE*=0.077)	**0.197(*SE*=0.092)***
Strategy	1.021(*SE*=2.383)	-0.134(*SE*=0.523)

***p*<.01 **p* ≤ .05 +*p*<.10

Note. Values are multilevel modeling coefficients (and standard error).

Table 4

Cross Level Interaction of Positive and Negative Schizotypy with SWM Performance (N = 369)

		Level 2 Predictors	
SWM Level 1 Criterion	Relation of Level 1 predictor and criterion	Step 1: Positive Schizotypy	Step 1: Negative Schizotypy
Between Errors	**1.649(*SE*=0.042)*** **	-0.404(*SE*=0.298)	0.290(*SE*=0.294)
Within Errors	**1.411(*SE*=0.171)*** **	-0.256(*SE*=1.322)	**-2.232(*SE*=1.001)***
Double Errors	**1.675(*SE*=0.232)*** **	-0.734(*SE*=1.417)	**-2.762(*SE*=1.206)***
Time to First Response	**0.117(*SE*=0.015)*** **	0.118(SE=0.080)	**0.221(SE=0.102)***
Time to Last Response	**10.052(SE=.166)*** **	0.898(SE=0.954)	1.105(SE=1.067)
Preparation time	**0.018(SE = 0.007)** **	0.042(*SE*=0.038)	**0.102(*SE*=0.048)***

***$p<.01$ **$p<.01$ *$p \leq .05$

Note. Values are multilevel modeling coefficients (and standard error)

Table 5

Direct Effects of Positive and Negative Schizotypy with SWM Performance (N = 311)

	Level 2 Predictors				
SWM Level 1 Criterion	Step 1: Positive Schizotypy	Step 1: Negative Schizotypy	Step 2: COMT	Step3: COMT X Positive Schizotypy	Step 3: COMT X Negative Schizotypy
Between Errors	**1.062(SE=0.400)****	-0.418(SE=0.388)	-0.051(*SE*=0.080)	0.279 (*SE*=0.586)	-0.031 (*SE*=0.565)
Within Errors	0.618(*SE*=1.156)	**2.127(*SE*=1.072)***	-0.007 (*SE*=0.227)	0.560 (*SE*=1.396)	-1.469 (*SE*=1.576)
Double Errors	1.304 (*SE*=1.276)	**2.612 (*SE*=1.298)***	0.110 (*SE*=0.268)	0.603 (*SE*=1.476)	**-3.836 (*SE*=1.934)***
Time to First Response	0.058 (SE=0.191)	0.292(SE=0.213)	0.024(SE=0.043)	-0.283 (*SE*=0.280)	0.295(SE=0.320)
Time to Last Response	0.778(SE=1.351)	2.203(SE=1.537)	0.238 (SE=0.325)	-1.822 (*SE*=1.868)	-0.209(SE=2.439)
Preparation	-0.025(0.084)	**0.170(SE=0.099)+**	0.018(SE=0.020)	-0.118(SE=0.117)	0.051(SE=0.155)
Strategy	1.024(SE=2.934)	-0.269(SE=0.920)	0.187(SE=0.685)	-0.065(SE=0.096)	-0.045(SE=0.102)

$^{**}p < .01$ $^{*}p \leq .05$ $^{+}p<.10$

Note. Values are multilevel modeling coefficients (and standard error)

Table 6

Cross Level Interaction of Positive and Negative Schizotypy with SWM Performance (N = 311)

		Level 2 Predictors				
SWM Level 1 Criterion	Relation of Level 1 predictor and criterion	Step 1: Positive Schizotypy	Step 1: Negative Schizotypy	Step 2: COMT	Step 3: COMT X Positive Schizotypy	Step 3: COMT X Negative Schizotypy
Between Errors	**1.646 (SE=0.045)*** **	-0.446 (SE=0.330)	0.429 (SE=0.313)	0.006 (SE=0.063)	-0.630 (SE=0.453)	0.016 (SE=0.437)
Within Errors	**1.418 (SE=0.186)*** **	-0.818 (SE=1.375)	-1.694 (SE=1.083)	0.131 (SE=0.253)	1.253 (SE=1.619)	0.624 (SE=1.459)
Double Errors	**1.733 (SE=0.270)*** **	-1.380 (SE=1.522)	-2.302 (SE=1.485)	0.071 (SE=0.306)	-1.502 (SE=1.838)	**4.221 (SE=2.010)***
Time to First Response	**0.120 (SE=0.017)*** **	0.112 (SE=0.089)	**0.260 (SE=0.117)***	0.020 (SE=0.026)	0.108 (SE=0.139)	-0.060 (SE=0.189)
Time to Last Response	**10.130 (SE=0.183)*** **	0.855 (SE=1.015)	1.297 (SE=1.174)	0.200 (SE=0.277)	-1.067 (SE=1.432)	-0.496 (SE=1.875)
Prep time	**0.020 (SE=0.008)****	0.017 (SE=0.039)	**0.147 (SE=0.052)****	0.008 (SE=0.012)	0.012 (SE=0.055	-0.072 (SE=0.077)

***p ≤ .001 **$p < .01$ *$p \leq .05$

Note. Values are multilevel modeling coefficients (and standard error)

Figure 1. Mean Positive and Negative Schizotypy Scores Associated with COMT Genotype.

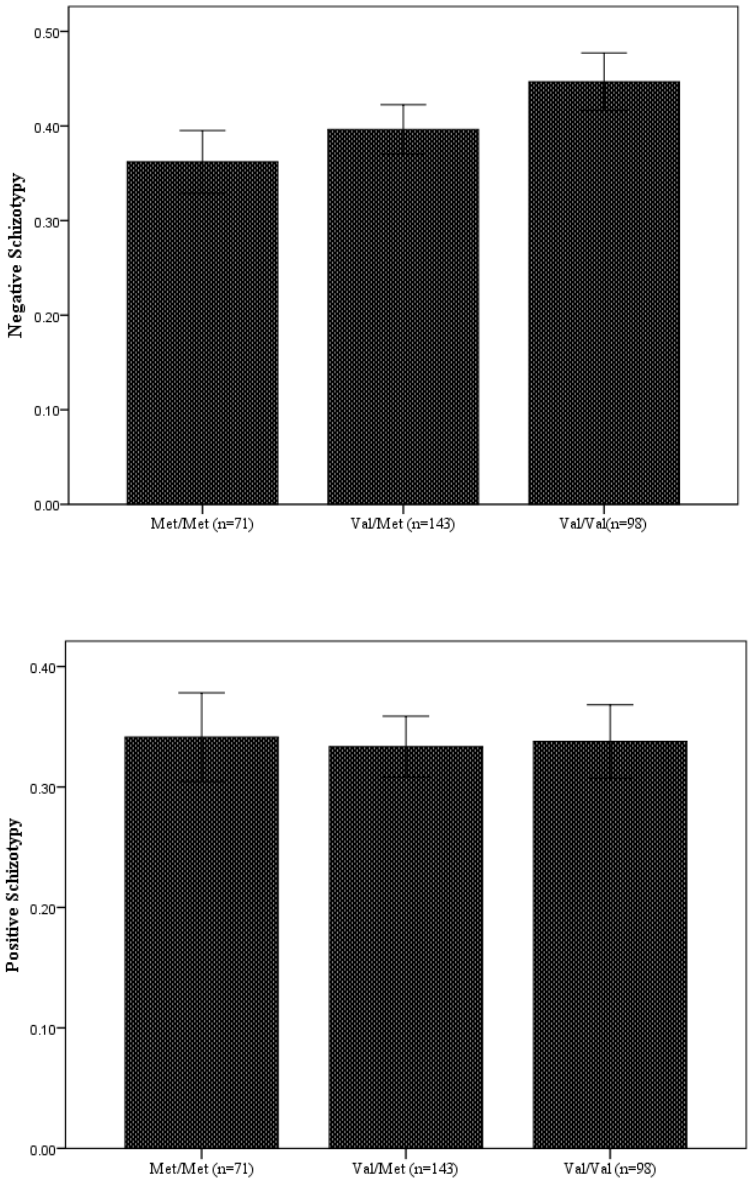

Figure 2. The Cross Level Interaction of Negative Schizotypy with Trial Type and Within Errors.

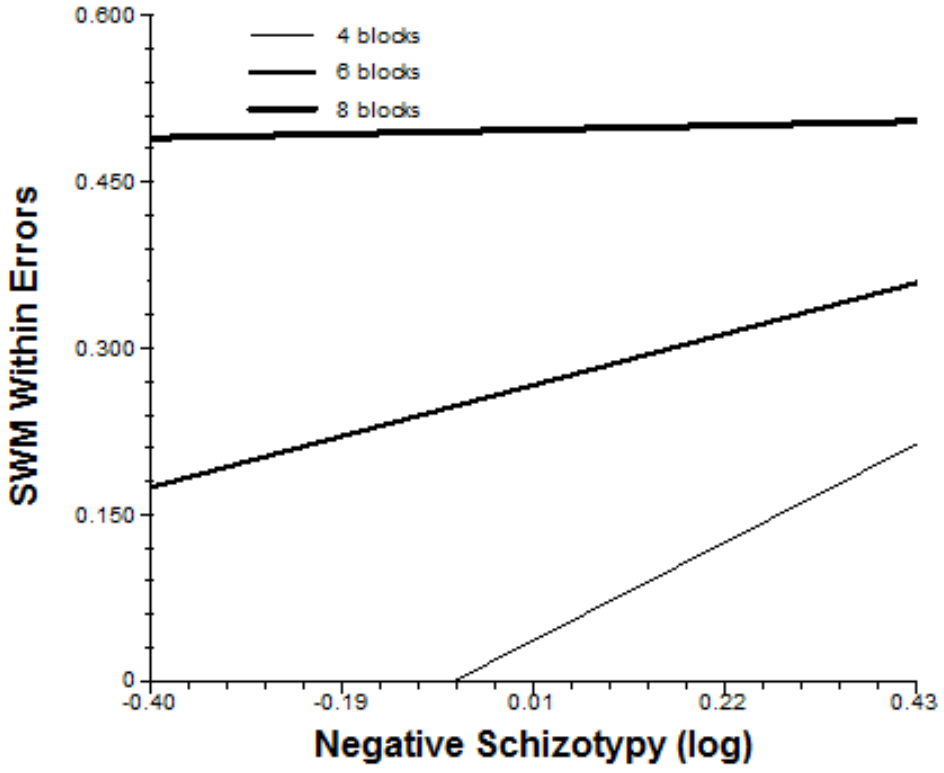

Figure 3. The Cross Level Interaction of Negative Schizotypy with Trial Type and Mean Time to First Response.