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Cognitive Performance in Schizophrenia and Schizotypal Personality Disorder:
The Influence of COMT and BDNF Polymorphisms

By

Hanan D. Trotman
Doctor of Philosophy

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Cognitive Performance in Schizophrenia and Schizotypal Personality Disorder: The Influence of COMT and BDNF Polymorphisms

By

Hanan D. Trotman

M.A., Emory University, 2006
B.S., Clemson University, 2003

Advisor: Elaine F. Walker, Ph.D.

An Abstract of
A dissertation submitted to the Faculty of the Graduate
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Abstract

The relation of the *Catechol-O-Methyltransferase Val108/158Met* (*COMT, rs4680*) and *Brain-Derived Neurotrophic Factor BDNF Val66Met* (*BDNF, rs6265*) polymorphisms with dopamine neurocircuitry and brain functions make them strong candidates for investigating the association between genes and cognitive function. Further, both of these polymorphisms have been implicated in risk for psychotic disorders, as well as cognitive impairment in psychosis. Nonetheless, findings on the association of these genes with cognition are mixed. Although the cumulative findings provide no consistent evidence to support an association of *COMT* or *BDNF* with vulnerability to psychosis, or of *COMT* with cognition, recent studies suggest an interactive effect of *COMT* and *BDNF* on cognitive performance. Based on these findings, the present study examined both the main and interactive effects of *COMT* and *BDNF* on cognition in schizophrenia-spectrum patients (patients diagnosed with psychosis or schizotypal personality disorder) and controls. The Logical Memory I and II and Letter-number Sequence subtests of the Wechsler Memory Scale, 3rd Edition (WMS-III) were administered. There was no main or interactive effect of the two polymorphisms on cognition within the schizophrenia-spectrum sample. Exploratory analyses revealed significant sex-specific effects; however, these were based on small subsamples, and should be interpreted with caution. Limitations of the present study, most notably the low frequency of *BDNF Met* carriers, constrained statistical power for detecting effects. The present findings highlight the complex nature of genetic effects on cognition.

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Cognitive Performance in Schizophrenia and Schizotypal Personality Disorder: The Influence of COMT and BDNF Polymorphisms

The modal developmental trajectory leading to schizophrenia and other psychotic disorders entails a gradual emergence of functional decline and subclinical symptoms in adolescence, with a clinical onset of psychotic symptoms in the early 20s (Thompson, Pogue-Geile, & Grace, 2004). Cognitive deficits are among the functional impairments associated with psychosis, and are most pronounced in the *schizophrenia-spectrum*, including schizophrenia (Ueland, Øie, Landrø, & Rund, 2004; McClellan, Prezbindowski, Breiger, & McCurry, 2004; Miclutia & Popescu, 2008) and schizotypal personality disorder (Cadenhead, Perry, Shafer, & Braff, 1999; Farmer et al., 2000; Roitman et al., 2000; Diforio, Walker, & Kestler, 2000; Siever et al., 2002; Harris, Minassian, & Perry, 2007; Gur et al., 2007; Voglmaier, Seidman, Salisbury, & McCarley, 1997). Individuals with schizophrenia and other psychotic disorders often manifest signs of cognitive impairment in childhood and adolescence, prior to the onset of their illness (Fuller et al., 2002; Ang and Tan, 2004; Erlenmeyer-Kimling et al., 2000), and some aspects of cognitive disturbance worsen with the onset of psychosis (Caspi et al., 2003) and with subsequent episodes (Braw et al., 2008). Because cognitive deficits are often present prior to illness onset and are not solely a secondary effect of symptoms, medication, or prolonged hospitalization, cognitive deficits are generally viewed as a core feature of schizophrenia (Gold, 2004; Joyce & Roiser, 2007; Hoff & Kremen, 2002) and a potential treatment target (Gold, 2004).

It is generally agreed that cognitive impairment is one of the most debilitating aspects of schizophrenia, and as such, is associated with a range of disabilities (Bell, Tsang, Greig, & Bryson, 2009; Brekke, Hoe, Long, & Green, 2007; Milev, Ho, Arndt, &

Andreasen, 2005). For example, cognitive impairment impacts an individual's real-world functional performance, including social, academic, and occupational function (Green, Kern, & Heaton, 2004; Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006). In individuals at high risk for schizophrenia, deficits in learning and memory are associated with impaired social functioning (Niendam et al., 2006). Reasoning and problem-solving deficits are also associated with global functioning impairment (Niendam et al., 2006).

Efforts have been long underway to understand the cognitive deficits associated with schizophrenia. However, this has been complicated by increasing evidence that schizophrenia is a heterogeneous clinical syndrome marked by heterogeneous cognitive profiles across individuals (Joyce & Roiser, 2007). Moreover, recent findings from genetic research indicate that vulnerability is likely a result of many genes with additive and interactive effects, and that there are nonspecific genetic vulnerabilities to psychosis, such that schizophrenia and affective psychoses share etiologic factors (Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2002). Thus, the focus of much research on cognitive deficit in psychosis has shifted to studies of the relation of candidate genes with various features of cognitive deficit. This work targets those domains of cognitive impairment (e.g., verbal and spatial working memory) that have been observed in all forms of psychosis.

Numerous studies have revealed associations between cognitive performance and various candidate genes in healthy participants (Posthuma, Cherny, & Boomsma, 2006) as well as individuals in the schizophrenia-spectrum (Tunbridge, Harrison, & Weinberger, 2006). In particular, studies demonstrate that polymorphisms in the *Catechol-O-Methyltransferase* (*COMT*) and *Brain-Derived Neurotrophic Factor* (*BDNF*)

genes influence cognition (Savitz, Solms, & Ramesar, 2006), and these variants are also proposed to be involved in the pathogenesis of schizophrenia (Harrison & Weinberger, 2005). Although findings on the relation of cognition with polymorphisms in the *COMT* and *BDNF* genes are mixed, the relation of these genes with dopamine neurocircuitry (Savitz et al., 2006; Goldman-Rakic, Castner, Svensson, Siever, & Williams, 2004) and functions of the prefrontal cortex (Savitz et al., 2006) and medial temporal lobe (Egan, Weinberger, & Lu, 2003) make them strong candidates for investigating the association between genes and cognitive function (Savitz et al., 2006; Ramus, 2006).

The present study is concerned with the relation of *COMT* and *BDNF* variants with cognitive deficits in schizophrenia spectrum disorders. Specifically, the focus is on adult patients diagnosed with schizophrenia and adolescents with schizotypal personality disorder (SPD). Research findings indicate that the *COMT* and *BDNF* genes play a role in the nature and severity of cognitive impairment in schizophrenia, although the relation may be interactive, and may vary as a function of the clinical characteristics of the sample (Dickinson & Elvevåg, 2009). Thus a clearer picture of the role of *COMT* and *BDNF* in the cognitive deficits associated with spectrum disorders may emerge from studies that include both individuals at clinical risk, namely youth with SPD, and adult schizophrenia patients.

To date there are only two published reports on *COMT* in patients diagnosed with SPD (Leung, McClure, Siever, Barch, & Harvey, 2007; Minzenberg et al., 2006) and no published report on the *BDNF* gene in schizotypal individuals. Further, most of the studies of *COMT* and SPD have focused on individuals toward the end of the risk period for schizophrenia (i.e., mean age of 30+ years), thus decreasing the proportion of the

sample likely to be later diagnosed with a psychotic disorder. In contrast, the adolescent SPD participants in the present study are known to be in the modal age period for the emergence of schizotypal syndromes that are associated with the onset of psychotic disorders in young adulthood. Finally, there is only one published report on the additive and interactive effects of *COMT* and *BDNF* on cognitive performance in the schizophrenia spectrum (Han et al., 2008). As described below, there is recent evidence that the *COMT Val*108/158*Met* polymorphism and the *BDNF Val*66*Met* polymorphism have interactive effects on cognitive function in both normal and clinical populations.

This paper begins with an overview of the schizophrenia spectrum, then a review of cognitive deficits in the schizophrenia spectrum is presented, and finally the literature on the relation of *COMT* and *BDNF* polymorphisms with cognition is examined. A description of the methodology for the current study is followed by study findings and a comparison of the current findings to the existing literature. A brief discussion of the implications and limitations of the current investigation is also provided.

Schizophrenia: Phenomenology and hypothesized etiology

Approximately 8% of the general population report psychotic experiences. But, only about 4% of individuals become impaired by these psychotic experiences (Howes & Kapur, 2009). Schizophrenia, the most severe and common psychotic disorder, is a phenotypically and etiologically heterogeneous syndrome. It is typically marked by a combination of positive symptoms (i.e., hallucinations, delusions), negative symptoms (e.g., social withdrawal, flat affect, decreased experience of emotion), and disorganized symptoms (e.g., thought blocking, tangential speech) (DSM-IV-TR, 2000; Criteria listed in Table 1).

It is well established that there are sex differences in the phenomenology of schizophrenia (Usall et al., 2001), although the lifetime risk of developing the illness is comparable for men and women (Häfner & an der Heiden, 1997). Men exhibit more pronounced negative symptoms (Aleman, Kahn, & Selten, 2003), poorer premorbid adjustment, greater prodromal features (Preston, Orr, Date, Nolan, & Castle, 2002), and an earlier age of onset (Iacono & Beiser, 1992). Research has also revealed more severe brain abnormalities in male schizophrenia patients (Hafner, 2003; Goldstein et al., 2002; Nopoulous, Flaum, & Andreasen, 1997). Women, in contrast, have a more benign course of illness, characterized by good prognostic indicators such as later age of onset, better premorbid functioning, and fewer negative symptoms (Salem & Kring, 1998).

Based on multiple lines of research, schizophrenia is assumed to originate from a constitutional vulnerability arising from interactions between environmental and genetic factors (Keshavan, Diwadkar, & Rosenberg, 2005). These gene-environment interactions impact, or interact with, normative neuromaturational processes during adolescence (Adams, 2000; Keshavan, Diwadkar, & Rosenberg, 2005), potentially causing a deviation from normal brain development (Feinberg, 1982; Keshavan, Anderson, & Pettegrew, 1994). This is presumed to be the underlying diathesis for schizophrenia (Walker & Diforio, 1997). For this reason, schizophrenia is viewed by many as a *neurodevelopmental disorder* (Brennan and Walker, 2001). Although brain changes continue beyond the adolescent period (Sowell, Thompson, Tessner, & Toga, 2001), across species, the adolescent period is characterized by rapid changes in brain development (Adams, 2000; De Bellis et al., 2001; Giedd et al., 1999; Spear, 2000;

Suzuki et al., 2005) and it is a period with an increased potential for development to go awry (Adams et al., 2000).

Neurodevelopmental aberrations are assumed to lay the groundwork for the abnormalities in neurotransmission that have been hypothesized to underlie the neuropathology of schizophrenia (Murray, McDonald, & Bramon, 2002; Tan, 2009). Glutamate, GABA, serotonin, and dopamine are the main neurotransmitters that have been implicated in schizophrenia. However, abnormalities in dopamine, more than any other neurotransmitter system, have received the most consistent support (Meltzer & Stahl, 1976; Carlsson, 1988; Winterer, 2007). It has been suggested that other neurotransmitter systems may be relevant primarily due to their effects on the dopamine system (Howes & Kapur, 2009).

The dopamine hypothesis for schizophrenia is based on accumulated evidence of its involvement in the pathogenesis of the disorder, as well as in its treatment. In a recent comprehensive review, Howes and Kapur (2009) conclude that it is presynaptic dopamine dysregulation that is the major site of dysfunction. They note the limited evidence for a causal relationship between low levels of cortical dopamine leading to elevations in subcortical dopamine. However, they argue for multiple causal pathways to increased striatal dopamine (e.g., genetic, neurodevelopmental, environmental, socio-cultural). They also review the compelling evidence that dopamine dysfunction is linked more broadly to psychosis, rather than specifically with schizophrenia (Howes & Kapur, 2009).

Maturational increases in dopamine activity during adolescence have been cited to account for the modal age at onset of schizophrenia and other psychoses (Benes, 2003).

Following the onset of puberty, there are significant developmental changes in brain structure and function, and these maturational changes may increase the likelihood of programmatic deviations. In particular, it has been suggested that aberrant connectivity and activity in dopamine circuitry may arise during adolescence and early adulthood, thus setting the stage for the onset of psychosis (Maccabe, 2008; Walker, 1994, 2002).

The period of functional decline that typically precedes the first episode of psychosis is referred to as the *prodrome*. As noted above, the *prodromal* syndrome usually becomes apparent in adolescence. The prodrome, which can last from months to several years, is characterized by subclinical manifestations of positive symptoms, including paranoia/suspiciousness and perceptual abnormalities, as well as subclinical negative symptoms such as social isolation and withdrawal, and nonspecific indicators of decline including impaired attention, depressed mood and decreased scholastic performance (Ang & Tan, 2004; Fuller et al., 2002; Lencz, Smith, Auther, Correll, & Cornblatt, 2004; Walker, Grimes, Davis, & Smith, 1993; Yung, Phillips, Yuen, & McGorry, 2004). As described below, SPD is among the prodromal syndromes that have been shown to precede the onset of psychosis (Miller et al., 2002; Miller et al., 2003; Woods et al., 2009). For most patients, the clinical course that follows the first psychotic episode includes significant impairment in social and occupational functioning (Jarbin, Ott, & Von Knorring, 2003, Schmidt, Blanz, Dippe, Koppe, & Lay, 1995).

Family, adoption and twin studies have long supported a genetic basis for at least some cases of schizophrenia as well as other psychotic disorders (Cardno & Gottesman, 2000; Sullivan, Kendler, & Neale, 2003). There is an elevated rate of affected individuals among biological relatives of probands, when compared to individuals in the

general population. For example, compared to the 1% rate of individuals in the general population with a lifetime diagnosis of schizophrenia, 6% of 1st degree relatives of affected individuals develop the disorder. Twin studies demonstrate that 12% to 17% of dizygotic twins and 30% to 50% of monozygotic twins with an affected co-twin develop the illness (Cardno & Gottesman, 2000). Taken together, these findings indicate that there are heritable genetic risk factors for psychotic disorders.

The risk for psychotic disorders is also elevated in individuals with a specific genetic disorder; namely, 22q11.2 deletion syndrome (DS). The 22q11.2 deletion is associated with a syndrome that entails a range of physical and behavioral disorders, including an increased rate of psychotic disorders (Murphy, Jones, and Owen, 1999). To date, 22q11.2 DS is the strongest genotypic predictor of schizophrenia, and some have suggested that 22q11.2 DS may be an etiologically distinct subtype of schizophrenia (Bassett & Chow, 1999). Nonetheless, the clinical presentation of these individuals is no less heterogeneous than in individuals without the deletion (Gothelf et al., 2007). Two percent of schizophrenia patients have been reported to have a deletion in the 22q11.2 region (Murphy, 2002; Karayiorgou et al., 1995), though more recent studies have showed lower risk (Horowitz, Shifman, Rivlin, Pisante, & Darvasi, 2005). In addition, of those that have the deletion, 25-32% eventually develop a psychotic disorder (Gothelf et al., 2007). Therefore a deletion in the 22q11.2 region is neither necessary nor sufficient for the development of schizophrenia. But interestingly, the deletion is much more common in individuals with child-onset schizophrenia---with nearly 7% of individuals with child-onset schizophrenia with the deletion in the 22q11.2 region (Usiskin et al., 1999). This supports the hypothesis that there is a greater genetic contribution to the

childhood development of characteristically adult-onset disorders (Nicolson et al., 2003; Nicolson & Rapoport, 1999; Liu et al., 2002). As described below, the *COMT* gene is in the region affected by the 22q11.2 deletion. This, in addition to other research findings, has led to interest in *COMT* as a risk gene for psychotic disorders.

Schizotypal Personality Disorder

Schizotypal Personality Disorder (SPD) is part of the odd or eccentric personality disorders (Cluster A), and characterized by positive (e.g., magical thinking, perceptual distortions, and ideas of reference) and negative (e.g., social withdrawal, flat affect) symptoms. It occurs in approximately 3% of the general population (DSM-IV-TR, 2000; diagnostic criteria listed in Table 2), but is more common in first degree relatives of schizophrenia patients (Tienari et al., 2003). In fact, the criteria for SPD were developed from research findings on symptom characteristics of biological relatives of schizophrenia patients (Spitzer, Endicott, & Gibbon, 1979). As is the case with other personality disorders, SPD is assumed to be a relatively stable syndrome (DSM-IV, 2000), although it is now known that it is often the syndromal manifestation of the prodrome to psychosis (Woods et al., 2009; Siever & Davis, 1991).

Individuals diagnosed with SPD are at greater risk for developing schizophrenia than individuals diagnosed with other personality disorders, including other Cluster A disorders (Siever et al., 2002). In fact, the greatest risk for psychosis is associated with SPD when criteria are met during adolescence (Klosterkötter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001; Miller et al., 1999; Woods et al., 2009). Among adults who are over 30 years of age, and have no Axis I disorder, those who meet SPD criteria are less likely to ever convert to a psychotic disorder (Häfner, Maurer, Löffler, & Riecher-

Rossler, 1993). Instead, most show stability in the pattern and severity of their SPD symptoms (Siever & Davis, 1991).

As noted above, SPD is one operational criterion for the schizophrenia prodrome (Woods et al., 2009). An SPD diagnosis encompasses subclinical versions of the positive and negative symptoms of schizophrenia. In addition to these, the prodromal syndrome often includes a variety of nonspecific symptoms such as sleep disturbances, irritability, and impaired tolerance to normal stress. It is estimated that between 25-45% of youth who meet criteria for the schizophrenia prodrome later develop schizophrenia (Miller et al., 2002; Yung et al., 2003).

It has been suggested that SPD is a more common phenotypic expression of the underlying neural diathesis for schizophrenia (Siever, Koenigsberg, & Reynolds, 2003; Walker & Diforio, 1997). Schizophrenia and SPD have therefore been conceptualized as lying on a continuum, ranging from relatively normal functioning to psychosis (Johns and van Os, 2001). In fact studies indicate that schizotypal traits, not meeting diagnostic criteria for SPD, are fairly common in the general population (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). These data are consistent with the concept of *schizotaxia*, proposed by Meehl to refer to the underlying substrate or "neural integrative defect" that can result in psychosis (Meehl, 1989). Schizotaxia, however, as a neurodevelopmental syndrome, is assumed to be present prior to the onset of prodromal symptoms (Tsuang, Stone, & Faraone, 2000).

Cognitive Impairment in the Schizophrenia Spectrum

Cognitive impairments have been documented across the schizophrenia-spectrum; however, researchers have struggled to account for the cognitive heterogeneity in the

spectrum (Joyce & Roiser, 2007). One key issue that has confronted research in this area is the distinction between specific cognitive deficits as opposed to a generalized cognitive deficit. The term "generalized" deficit has been used to refer to impairment that occurs across all domains of cognitive functioning, whereas "specific" refers to an impairment that is exclusive to, or more pronounced in, one functional domain. Thus, it has been argued that a specific cognitive deficit must be demonstrated independently from a generalized deficit to conclude that a particular domain of functioning is uniquely impaired (e.g., differential deficit; Chapman & Chapman, 1973).

Moreover, early research on cognition in schizophrenia emphasized the goal of identifying deficits that were unique to schizophrenia (Cohen, Barch, Carter, & Servan-Schreiber, 1999), with the implicit assumption that a specific type of cognitive impairment subserved psychotic symptoms (Rund, 1998). With the accumulation of research findings over decades, it is now apparent that the characteristic performance for groups of patients are below average on virtually all cognitive tasks, including general intellectual measures (Aylward, Walker, & Bettes, 1984). Thus, the modal pattern of cognitive deficit in schizophrenia entails below average performance on most cognitive measures.

A recent review concludes that generalized cognitive deficit is a core feature of schizophrenia (Dickinson & Harvey, 2008), as impairment is found in nearly every cognitive domain and across clinical states and time periods. Nonetheless, this does not rule out the presence of subgroups of patients with specific, or non-generalized, cognitive impairments. Nor does it rule out the possibility that certain domains of cognitive function are characterized by more pronounced impairment than others. In fact, as

described below, it appears that working memory shows relatively greater impairment than other cognitive domains in schizophrenia (Elvevåg & Goldberg, 2000; Lee & Park, 2005). Working memory is defined as "…processes that support the short-term maintenance or manipulation of relevant information when it is no longer present…" (Gibbs & D'Esposito, 2005).

Demonstrating specific deficits continues to be an ongoing challenge (Chapman & Chapman, 1973, 2001). Most assessment instruments measure general cognitive ability, or at the very least other related cognitive functions, in addition to the domain of interest, and thus do not strictly assess separable cognitive domains (Dickinson & Harvey, 2008; Knight & Silverstein, 2001). Another challenge that arises in the demonstration of a specific deficit is differences among tests' discriminative power (e.g., how well the test differentiates between two groups based on ability). If tests differ on this characteristic, spurious findings could result (Chapman & Chapman, 1973). Specifically, less discriminating tests may fail to identify impairment that would otherwise be captured by a test with more discriminative power (Chapman & Chapman, 1973). These factors must be taken into consideration when drawing inferences from research on cognition in psychiatric disorders.

Schizophrenia

Cognitive deficits in schizophrenia are independent of medication and institutionalization, and are often present before clinical onset (Ang & Tan, 2004; Hoff & Kremen, 2002; Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000; Kremen, Seidman, Faraone, & Tsuang, 2001). In addition, there is evidence of a cognitive decline that precedes the onset of the illness (Tan & Ang, 2001), although cognitive deficits appear to

remain fairly stable during the initial stages of schizophrenia (Albus et al., 2002; Hughes et al., 2003). There is evidence, however, that schizophrenia patients experience decrements in cognitive performance later in life (i.e., after 65), with a magnitude greater than what is expected as part of normal aging process (Aleman, Hijman, de Haan, & Kahn, 1999; Friedman et al., 2001). This suggests that the cognitive decline seen in elderly schizophrenia patients partially reflects the illness process, and is not solely attributable to aging.

Schizophrenia patients have deficits in virtually all cognitive domains (Dickinson and Harvey, 2008), including impairments in attention (Lieh-Mak & Lee, 1997; Harris et al., 2007), executive function (Weickert et al., 2000), verbal declarative memory (Kremen et al., 2001) and verbal fluency (Docherty et al., 1996). Similarly, recent research has shown that patients with the 22q11.2 DS who also meet diagnostic criteria for schizophrenia have impaired performance on measures of spatial working memory and strategy formation, similarities, visual recognition, and attention (van Amelsvoort et al., 2004).

For some schizophrenia patients, impairment appears to be confined to a specific functional domain (e.g., attention, working memory, executive function), in contrast to an overall generalized cognitive deficit (Hoff & Kremen, 2002; Weickert et al., 2000). For example, some patients show deficits on attention and/or executive function tasks, yet exhibit normal performance on general intelligence measures (Weickert et al., 2000). Further, it has been estimated that 27% of patients fall within or above the average range of neuropsychological function (Palmer et al., 1997). This finding, however, does not suggest that patients scoring within the normal range have not experienced a decline.

Cognitive impairment is correlated with symptom severity in schizophrenia (Bilder et al., 2000; Mohamed, Pausen, O'Leary, Arndt, & Andreasen, 1999). A meta-analytic review concluded that negative and disorganized symptoms are associated with greater executive functioning deficits (Nieuwenstein, Aleman, & de Haan, 2001). Negative symptoms, in particular, show an inverse correlation with sustained attention (Nieuwenstein et al., 2001) and long-term and short-term memory (Aleman et al., 1999). In line with sex differences in symptom presentation, male patients show significantly greater impairment than female patients on measures of attention, language, verbal memory, and executive function (Goldstein, Allen, & van Kammen, 1998).

As stated above, working memory is one of the most consistently impaired domains in schizophrenia (Lee & Park, 2005; van Snellenberg, 2009). Similarly, schizophrenia patients demonstrate context-processing deficits (Cohen et al., 1999) that are not improved following psychopharmacological treatment, as in other psychotic disorders (Barch, Carter, MacDonald, Braver, & Cohen, 2003) nor are they related to treatment delay (e.g., DUP) in first episode patients (Miclutia & Popescu, 2008)

In summary, cognitive impairments are strongly associated with schizophrenia; they are present before the onset of symptoms, persist through the course of the disorder, and may worsen with advanced age. Further, cognitive impairments do not appear to routinely result from medication or institutionalization. In fact, some atypical antipsychotic medications have been shown to improve cognitive performance (Purdon, 1999; Weickert et al., 2003; Barch et al., 2004; Siegel et al., 1996), with the exception of specialized working memory deficits (Barch et al., 2003). Finally, there is considerable evidence that verbal working memory is the area of greatest impairment.

SPD

SPD patients exhibit cognitive deficits that are less severe, yet parallel those observed in schizophrenia patients. An extensive body of research has established that individuals with SPD display cognitive impairments in a range of domains, including attention, executive function, verbal learning, abstraction, mental flexibility, verbal and visuospatial working memory (Siever et al., 2002). SPD individuals also perform below the general population on measures of intellectual functioning (Cadenhead et al., 1999). However, studies vary in their operational definition of "intelligence." Some studies focus mainly on verbal intelligence, while others use nonverbal intelligence measures, and still other studies assess intelligence with a composite of verbal and nonverbal intelligence. The variable definitions of "intelligence" have implications for research findings. For example, Roitman et al. (2000) found that SPD participants performed comparable to normal control participants on verbal measures of general ability, but were significantly impaired compared to normal control participants on nonverbal measures. Attentional impairments are also observed in SPD (Roitman et al., 1997; Chen et al., 1998) and may be a partial explanation of other cognitive deficits (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005).

In addition to evidence of lower intelligence, individuals with SPD manifest more pronounced deficits in some specific domains, including measures of executive function, such as the modified Wisconsin Card Sorting Task (Diforio et al., 2000). As is the case with schizophrenia, the most consistently demonstrated cognitive deficit in SPD is working memory impairment (Cadenhead et al., 1999; Roitman et al., 2000; McClure et al., 2007). Not only do SPD individuals exhibit working memory deficits compared to

normal participants, but these deficits are also present relative to individuals with Cluster B and C personality disorders (Farmer et al., 2000; Roitman et al., 2000).

Memory impairment in SPD does not disappear when controlling for general intellectual abilities (Roitman et al., 2000) (and may be a specific deficit, thus, the controversy discussed above), nor do these deficits appear to be due to the presence of major depression (Roitman et al., 2000; Mitropoulou et al., 2002) or psychiatric medication (Roitman et al., 2000). But the story may be more complicated than specific vs. generalized deficits. For example, both verbal and nonverbal memory are affected in SPD (Siever et al., 2002), and it appears that verbal memory deficits are the most pronounced and may underlie deficits in other cognitive domains (Voglmaier et al., 2000).

The similarities in cognitive impairment between schizophrenia and SPD are quite striking. However, by definition, individuals with SPD do not manifest the clinical symptoms of psychosis, and as would be expected, exhibit less severe cognitive disturbances (Cadenhead et al., 1999; Siever et al., 2002; Trestman et al., 1995). Nonetheless, it appears that the patterns of cognitive deficits are similar for schizophrenia and SPD.

Genetic Vulnerability and Cognition in schizophrenia spectrum disorders

As noted above, it is widely accepted that genetic factors contribute to the liability for both schizophrenia and SPD (Kety et al., 1994; Glatt, Faraone, & Tsuang, 2007; Wynne et al., 2006). Further, family, twin and adoption studies have demonstrated the genetic link between SPD and schizophrenia (Nicolson et al., 2003; Tienari et al., 2003). For example, SPD is more common in adopted-away children of mothers with a

schizophrenia-spectrum disorder than in adopted-away offspring of non-schizophrenia-spectrum mothers (Tienari et al., 2003). Similarly, families of patients with SPD have an increased incidence of schizophrenia-related disorders as well as schizophrenia itself (Battaglia, Bernardeschi, Franchini, Bellodi, & Smeraldi, 1995). Likewise, the likelihood of having a relative with SPD is comparable whether an individual is diagnosed with SPD or schizophrenia (Silverman et al., 1993). Other findings indicate that parents of children with schizophrenia have a higher risk of schizophrenia-spectrum disorders than parents of children without psychosis (Nicolson et al., 2003). Furthermore, parents whose offspring had childhood-onset schizophrenia had a greater risk of a schizophrenia-spectrum disorder than parents of adult-onset patients (Nicolson et al., 2003). This finding is in line with the notion that childhood onset of disorders typically manifested in late adolescence/early adulthood is an indication of greater genetic risk (Nicolson et al., 2003; Nicolson & Rapoport, 1999; Liu et al., 2002).

There is evidence to suggest that some of the same genetic factors that confer risk for schizophrenia may also give rise to the cognitive deficits associated with the illness. Asarnow and colleagues (2002) found that non-psychotic children from the community with a 1st or 2nd degree relative with schizophrenia, schizoaffective disorder, paranoid personality disorder, or SPD had poorer intellectual functioning, decreased performance on expressive and receptive vocabulary, decreased motor speed, and problems with visual-motor coordination compared to children from the community without a family history of a schizophrenia-spectrum disorder. Further, healthy (i.e., no psychiatric disorder) relatives of schizophrenia patients show deficits in sustained attention (Chen et al., 1998), verbal working memory (Conklin, Curtis, Katsanis, & Iacono, 2000; Sitskoorn

et al., 2004) and executive function (Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004), again suggesting that cognitive deficits reflect a genetic liability for the illness. A study of monozygotic twin pairs provides further evidence for this point; unaffected twins from discordant twin pairs had attenuated performance on measures of memory and executive function compared to normal twins, where neither member of the pair was affected by schizophrenia (Goldberg et al., 1995). In addition, siblings demonstrate intermediate performance to first-episode patients and controls on verbal memory, visuospatial explicit memory, spatial short-term memory, and spatial working memory (Miclutia & Popescu, 2008).

Genetic Mechanisms in Schizophrenia Spectrum Disorders

It is now abundantly clear that, from a genetic standpoint, schizophrenia is a *complex* human disease. Complex, in this manner, refers to the recognition that the genetic transmission of schizophrenia does not follow basic Mendelian principles (Lander & Schork, 1994; Craddock, O'Donovan, Owen, 2007). Instead, it appears that schizophrenia and other psychotic disorders are the consequence of multiple genetic and environmental factors. The same holds for all domains of cognitive function.

Genetic researchers have acknowledged the inherent complexities in the study of genes and behavior. One gene can affect several processes, genes can modify the expression of other genes, and multiple genes can additively or interactively affect a single process (Goldberg & Weinberger, 2004). A brief review of the complex genetic issues related to the transmission of schizophrenia and associated cognitive deficits, including linkage disequilibrium (in genetic association) and population stratification, is presented below.

Genetic Association in Complex Disease

Mendel formulated the *fundamental principles of inheritance*; two components are most salient to the study of complex diseases. The first component, the *law of segregation*, is that alleles separate from each other in germ cells during meiosis and are packaged into separate gametes. Thus each gamete receives only one copy or allele of each gene, and the alleles segregate in the germ cells in equal proportions (i e. Mendelian ratios) (Pasternak, 2005; Lewis, 2007).

The second, the *law of independent assortment* is that alleles of different genes assort independently of one another during gamete formation. But we now know that this is true only for genes that are not 'linked' to each other. Linkage refers to the association of two or more loci on a chromosome with limited recombination between them. In other words, genes that are in close proximity on the same chromosome are more likely to be inherited together, as they are less likely to separate (likelihood of recombination is minimized) during meiosis, and are thus packaged in a single gamete. This is the concept of genetic linkage. In other words, linkage is the co-segregation of genes on the same chromosome in a nonrandom fashion and can be described as a "violation" of Mendel's second law. In research on disease, linkage is demonstrated in pedigrees when a genetic marker segregates with the disease phenotype throughout a family. In some situations, a particular genetic marker is close enough to the locus for the disease gene(s) that the likelihood of recombination is minimized. When two loci are "linked" the proportion of recombinant gametes is significantly less than the random expectation, ½ (Pasternak, 2005; Lewis, 2007).

Another factor to consider is that genes can be pleiotropic, that is, one gene can influence for multiple phenotypes. One set of mechanisms involved in pleiotropy, for example, is that a gene codes for a product that influences different cells in different ways, or has a signaling function on various targets. An additional factor contributing to non-Mendelian patterns of inheritance is polygenicity, which occurs when two or more genes contribute to the expression of a phenotype characteristic (trait) (Kovas & Plomin, 2006).

Allelic association is another relevant concept. It refers to the excessive co-occurrence of certain combinations of alleles in a population of gametes, and does not require the observation of parental transmission. Alleles are said to be "associated" if the occurrence of allele X in a gamete is not independent of the occurrence of allele Y in the same gamete. The demonstration of association in a population however, is affected by allele frequency and particular aspects of the study population (Pasternak, 2005; Lewis, 2007).

The occurrence of linkage in the context of association results in *linkage disequilibrium*. Linkage disequilibrium is the non-random association of alleles at two or more loci, on the same chromosome. In other words, linkage disequilibrium occurs when different alleles occur together in a nonrandom fashion (greater than chance level) (Pasternak, 2005; Lewis, 2007).

Population stratification

Inconsistent findings in genetic studies are often attributed to *population stratification* (Hutchinson, Stallings, McGeary, & Bryan, 2004), which occurs when there is a systematic difference in allele frequencies between subpopulations, usually due to

different ancestry, and there is also a coincidental different in phenotype (Heiman, Hodge, Gorroochurn, Zhang, Greenberg, 2004). Population stratification can be a major problem in genetic studies because it can produce spurious associations (type I error) or, "population level associations between a marker and phenotype in which the phenotypic variation is not caused by genetic variation at the marker or any locus linked to the marker" (Redden & Allison, 2006, pg. 678).

Two conditions must be met for population stratification to occur: 1) the allele frequency of a given marker must differ between the subgroups in the population studied, and 2) the same subgroups must differ on the outcome variable (Hutchinson, et al., 2004). Often when subgroups of a sample differ with regard to ethnicity, differences in allele frequencies are present. In fact, allele frequencies for the *COMT Val/Met* polymorphism differ by ethnic group, with Europeans having near equivalent frequencies of the *Val* and *Met* alleles, while the *Val* allele is more common than the *Met* allele across most other ethnic groups (Palmatier, Kang, & Kidd, 1999).

The probability of spurious association produced by a stratified sample depends on "the magnitude and direction of the association between the genetic variable and population subgroups" (Hutchinson et al., 2004, pg. 68). Researchers attempt to prevent spurious associations by statistically testing for the effects of ethnicity or by testing ethnically homogeneous groups. Nonetheless, these methods do not always solve the problem, and spurious associations occur even within small seemingly homogeneous subgroups (Redden & Allison, 2006).

Phenotypic Heterogeneity and the Endophenotype Approach

It is now generally assumed that the phenotypic heterogeneity in schizophrenia and the pleiotropic nature of genes make it unlikely that a direct association will be found between the schizophrenia syndrome and one or a small subset of genes (Jablensky, 2006; Craddock et al., 2007). Inconsistent findings in the literature undoubtedly reflect the inherent challenges in linking genetic variants to psychiatric conditions (Galderisi et al., 2005). Endophenotypes are one proposed solution to this problem.

An endophenotype, as conceptualized by Gottesman and Gould (2003), is a vulnerability indicator associated with the illness state that is heritable, but at least partially independent of acute symptoms. By definition, a vulnerability or risk marker must also co-segregate with the illness within families (linkage) and be present in unaffected relatives at a rate greater than within the general population. Additional criteria for defining an endophenotype include the presence of good psychometric properties, a relationship with the disorder and its symptoms in the general population, stability over time, that is independent of symptoms, shared underlying genetic influences with the disorder, association and/or linkage with candidate genes or loci associated with the disorder, and association with the gene over and above the gene's association with the disorder or its symptoms, mediation and moderation (Bearden & Freimer, 2006; Waldman, 2005; Kéri & Janka, 2004; Viding & Blakemore, 2007).

The term endophenotype is often used interchangeably with "intermediate phenotype." The term intermediate phenotype is often favored because it illustrates the level of analysis (i.e., *intermediate*) of the risk marker between the gene and the disease state. An intermediate phenotype, like an endophenotype, is a trait or characteristic of the

disease state that is closer to the gene than the disorder itself. For simplicity, I use the term *endophenotype* throughout this paper.

Research attempting to link genes to psychiatric disorders suggest that target genes probably impact endophenotypes, rather than having direct effects on the disease (Goldberg & Weinberger, 2004). For example, it is plausible that genes impacting neurodevelopment cause structural and functional changes in the brain that make individuals vulnerable to disease. In part, because endophenotypes are hypothetically "closer" to the gene, effects of smaller magnitude can potentially be detected and this can provide a window into underlying pathology (Braff, Freedman, Schork, & Gottesman, 2007).

There are multiple putative endophenotypes (e.g., P50 Suppression, Prepulse Inhibition, Smooth-Pursuit Eye Movement, Antisaccade, Executive Functioning, Thought Disorder, and P300 Event-Related Potential; Braff & Freedman, 2002) in genetic studies of schizophrenia. Working memory impairment is another example of a commonly studied endophenotype in schizophrenia (Braff & Freedman, 2002; Glahn et al., 2003). Gur (ICOSR conference, 2009) proposed that the same liability that accounts for schizophrenia also accounts for neurocognitive deficits in the disorder. This notion, however, may be valid without the assumption that the relationship between schizophrenia and its underlying genes are mediated through neurocognitive deficits. Gur presented data demonstrating that the degree of genetic relatedness was associated with similarity in performance among unaffected relatives. That is, the more removed an individual was from the affected family member, the less impaired their cognitive function. Although, we often conceptualize endophenotypes as risk markers for illness,

Braff (ICOSR conference, 2009) also advocated for the endophenotype approach in identification of protective factors, suggesting that protective genes in unaffected relatives may contribute to reduced penetrance. Once markers are accepted as endophenotypes continued evaluation of the validity and utility of these markers is generally not addressed.

Catechol-O-Methyltransferase (COMT) Val108/158Met Polymorphism

The Catechol-*O*-Methyltransferase (*COMT*) gene (Figure 1) is located in the 22q11.2 micro-deletion region (associated with schizophrenia susceptibility) and codes for the enzyme that catalyses the methylation of catechols—which results in the breakdown of catecholamines (e.g., dopamine, norepinephrine, and epinephrine). *COMT* regulates synaptic dopamine primarily in the prefrontal cortex because of the lack of dopamine transporters, but *COMT* is less active in areas like the striatum because of sufficient dopamine transporters (Chen, Lipska, et al., 2004; Meyer-Lindenberg et al., 2005).

A transition from guanine to adenine results in a substitution from Valine (*Val*) to Methionine (*Met*) at codon 158 on the membrane-bound form (or codon 108 on the soluble form) (Lotta et al., 1995). This change in amino acid subsequently results in heat liability and low enzyme activity (Lachman, et al., 1996). In other words, the codon 108/158 polymorphic change in thermostability (temperature sensitivity) also leads to the functional variations in *COMT* (i.e., *Val* homozygotes have increased activity of *COMT* in their blood compared to *Met* homozygotes) at normal body temperature (Lachman et al., 1996). Early studies suggested that *Met*, or the heat-labile low activity allele, had three to four times lower enzyme activity, but later studies demonstrate a two-fold

difference in enzyme activity (Shield, Thomas, Eckloff, Wieben, & Weinshilboum, 2004). Chen, Lipska, and colleagues (2004) demonstrate that the enzyme activity of the *Val* variant is approximately 40% higher than that of the *Met* variant at normal body temperature in the dorsal prefrontal cortex of post-mortem brains. Co-dominance of the *COMT* alleles results in intermediate enzyme activity in heterozygous individuals. The *Val108/158Met* has been shown to impact protein abundance and enzyme activity, while other single nucleotide polymorphisms (SNPs) studied in the *COMT* gene (specifically, rs737865 and rs165599) do not affect protein abundance or enzyme activity (Chen, Lipska, et al., 2004).

COMT and risk for schizophrenia.

Early studies of the *COMT* functional polymorphism and schizophrenia suggested no or modest association in risk for schizophrenia (Li et al., 1996). Subsequently, several research groups reported that the *COMT Val* allele was associated with greater risk for schizophrenia (Egan et al., 2001; McIntosh et al., 2007), but other studies failed to replicate these findings (Park et al., 2002; Shifman et al., 2002; Fan et al., 2005; Männisto & Kaakkola, 1999; Chen, Wang, O'Neill, Walsh, & Kendler, 2004; Handoko et al., 2005) and some studies even suggested that it was the *Met* allele that increased risk (Park et al., 2002; Sazci et al., 2004; Ohmori et al., 1998; Kotler et al., 1999; Bilder et al., 2002).

Since 2003, several meta-analyses of the relation of *COMT* with risk for schizophrenia or other psychoses have been conducted, and the results have been consistent in suggesting no association with *Val108/158Met* or other *COMT* SNPs (Allen et al., 2008; Fan et al., 2005; Glatt, Faraone, & Tsuang, 2003; Okochi, et al., 2009). The

meta-analysis by Glatt and colleagues (2003) supports the prevailing view that there is no association between *COMT Va108/158Met* and risk for schizophrenia in case control studies, however, in their analysis of five family-based studies, they found an association between the *Val* allele and risk for schizophrenia, though it should be noted that only 2 out of the 5 studies reported a significant association (Glatt et al., 2003). However, subsequent meta-analyses conducted on the relation of *COMT* and schizophrenia, indicate no significant association between *COMT* and risk for schizophrenia, particularly after removing problematic studies (i.e., studies with departure from Hardy-Weinberg equilibrium) (Munafo, Bowes, Clark, & Flint, 2005; Craddock, Owen, & O'Donovan, 2006). Although it appears that *COMT Val108/158 Met* is not associated with risk for schizophrenia, it has been suggested that it may be in linkage disequilibrium with the causal variant, which could explain the inconsistent findings (Shifman et al., 2002).

In addition, it is possible that gene-environment interactions also contribute to the inconsistent findings in the literature. For example, in a longitudinal study of a birth cohort, *Val* carriers were more likely to develop psychosis if they smoked cannabis, but this same effect was not true for homozygous *Met* individuals (Caspi et al., 2005). In addition, individuals with at least one *Val* allele appear to be more susceptible to the psychogenic effects of cannabis (Henquet et al., 2006). Thus, it is possible that *Val* carriers are more vulnerable to psychosis in samples with high rates of exposure to cannabis. It is also of interest that another report suggests that individuals with schizophrenia homozygous for the *Val* allele have an earlier age of onset for the illness than homozygous *Met* individuals (Galderisi et al., 2005; Pelayo-Teran, et al., 2008).

COMT and cognition in schizophrenia

Although *COMT Val108/158Met* appears to have no significant relation with risk for schizophrenia, several lines of evidence across various psychiatric populations suggest that *COMT* is associated with cognitive functioning (Egan et al., 2001; Galderisi et al., 2005; MacDonald, Carter, Flory, Ferrell, & Manuck, 2007; Shashi et al., 2006). In particular, most studies suggest that the *Val* allele is associated with poorer performance on frontally-mediated tasks (working memory, executive function, attention) (Egan et al., 2001; Malhotra et al., 2002; Rosa et al., 2004; Bilder et al., 2002; Aguilera et al., 2008), and this finding remains fairly consistent in patients with schizophrenia, psychotic disorders, individuals at risk for psychosis (Minzenberg et al., 2006; Leung et al., 2007; Ehlis, Reif, Herrmann, Lesch, & Fallgatter, 2007; Galderisi et al., 2005; Goldberg et al., 2003; Bilder et al., 2002; Nolan, Bilder, Lachman, & Volavka, 2004; Woodward, Jayathilake, & Meltzer, 2007; Egan et al., 2001), healthy individuals (Aguilera et al., 2008; Barnett, Jones, Robbins, & Muller, 2007; MacDonald et al., 2007; Malhotra et al., 2002; Goldberg et al., 2003; Diamond, Briand, Fossella, & Gehlbach, 2004), and individuals with 22q11.2 DS (Bearden et al., 2004; Kates et al., 2006). The association between the *COMT Val* allele and frontally-mediated tasks has been attributed to reduced frontal dopamine activity in *Val* carriers. Although a recent meta-analysis of research on *COMT* and cognition did find support for a relation of the *COMT Val* allele with deficit performance on the WCST in normal individuals, the relation was not significant for samples of schizophrenia patients (Barnett et al., 2007). It should be noted that this meta-analysis was specific to studies utilizing the WCST preservative errors as the outcome measure of cognitive function. The WCST is a specific measure of executive capacity that includes multiple functions; if the authors had included studies across multiple

cognitive measures capturing executive function, different results may have been revealed.

However, despite this general trend, some studies report that poorer cognitive performance is associated with the *COMT Met* allele in participants at risk for psychosis (Krabbendam et al., 2006), in Parkinson's patients (Foltynie et al., 2005; Williams-Gray, Hampshire, Barker, & Owen, 2008), in individuals with ADHD (Bellgrove et al., 2005), in some 22q11.2DS samples (Gothelf et al., 2005), in healthy individuals taking standardized tests (Yeh, Chang, Hu, Yeh, & Lin, 2009), and in schizophrenia patients (Neuhaus et al., 2009; Ho et al., 2005). It should be noted, however, that in the Neuhaus et al. (2009) study of schizophrenia patients, the allele frequencies deviated from Hardy-Weinberg expectation. Finally, it is not surprising, given the complex nature of genetic effects, some studies fail to find an association between *COMT Val/Met* and cognition (van Amelsvoort et al., 2008; Dennis et al., 2010; Ho et al., 2005; Tsai, Hong, Hou, & Yen, 2006; Stefanis et al., 2004; Smyrnis et al., 2007).

Researchers have struggled to explain why some studies find the *Val* allele to impart poorer performance, others find the *Met* allele to be linked with deficits, and others fail to find an association. Recent reviews of this body of research (Tunbridge et al., 2006; Dickinson & Elvevåg, 2009) have now focused on the complex relation between dopamine and cognition, noting the extensive evidence of an 'inverted U' relation (Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). Specifically, dopamine receptor stimulation in prefrontal cortex produces an 'inverted-U' dose-response, whereby either too little or too much stimulation impairs working memory. This response has been observed across species, with a variety of dopamine agonists and

antagonists (Cai & Arnsten, 1997; Zahrt, Taylor, Mathew, & Arnsten, 1997; Lidow, Koh, & Arnsten, 2003). The cellular basis for the inverted-U has been observed in PFC neurons of behaving monkeys: moderate levels of dopamine receptor stimulation optimize cognitive functioning by reducing distractibility, whereas low and high levels impair performance (Vijayraghavan, et al., 2007).

In an experimental demonstration of this effect in relation to *COMT* genotype, normal participants' task performance and frontal activity on fMRI were measured under varying cognitive loads (n-back task) and with/without amphetamine challenge (Mattay et al, 2003). While *Val* carriers manifested lower working memory performance under baseline conditions, amphetamine enhanced the efficiency of their prefrontal cortex function during a working memory task, presumably because these participants have relatively less prefrontal synaptic dopamine. In contrast, in participants with the low activity *Met*/*Met* genotype, who tended to have better baseline prefrontal function, amphetamine had no effect on performance at low-to-moderate working memory load, but caused deterioration at high working memory load.

Drawing on this model, Dickinson and Elvevåg, (2009) show how the pattern of research findings on *COMT* and cognition conform to the inverted-U model. For example, the relative performance advantage of healthy *Met* carriers varies as a function of cognitive demands, and presumably the cortical activation effects of the task (Nolan et al., 2004). They conclude that, in healthy research participants with moderately difficult cognitive tasks, the *COMT Met* allele carriers show a performance advantage, consistent with the notion that higher mean cortical dopamine activity is beneficial in healthy participants. Among schizophrenia patients, *COMT Met* carriers also manifest an

advantage, although it is less consistent and less pronounced, possibly because dopamine activity is elevated in the disorder. Dickinson and Elvevåg, (2009) also discuss the possible influence of developmental stage on the relation of *COMT* with cognitive functions, as normative cortical dopamine activity changes over the life span (Volkow et al., 2000). Finally, they note the likely interaction between *COMT* and other genes that influence cognition, such as the Brain-Derived Neurotrophic Factor gene.

Brain-Derived Neurotrophic Factor (BDNF) Val66Met Polymorphism

Similar to *COMT*, brain-derived neurotrophic factor (*BDNF*) *Val66Met* (Figure 2) is a genetic variant that has been linked with schizophrenia and has been shown to effect dopamine regulation (Guillin, Demily, & Thibaut, 2007; Pang & Lu, 2004; Angelucci, Brenne, & Mathe, 2005). The *BDNF* gene is located on chromosome 11p12 (3) and codes for proBDNF (precursor peptide to *BDNF*). *BDNF* is part of the neurotrophin family and implicated in neural development (Hyman et al., 1991; Poo, 2001). It is particularly important for neurogenesis, including the differentiation of dopamine neurons during brain development (Angelucci et al., 2005), and the development and survival of these neurons (Pang & Lu, 2004; Angelucci et al., 2005).

*BDNF Val*66*Met* is located at nucleotide 196 and produces an amino-acid substitution, from Valine to Methionine at codon 66. The *Val* to *Met* substitution occurs in the 5' prodomain region of *BDNF* (Seidah, Benjannet, Pareek, Chretien, & Murphy, 1996), and is suspected to impact function because it alters trafficking and secretion of the *BDNF* protein (Chen, Patel, et al., 2004). The homozygous *Val* genotype is associated with higher *BDNF* secretion and intracellular trafficking of *BDNF* (Egan, Kojima et al., 2003), and there is evidence that inhibition of the *BDNF* gene may trigger long-term

potentiation (LTP) deficits (Egan, Kojima et al., 2003). In contrast, *Met* carriers are thought to have impaired LTP, partly resulting from lower intracellular trafficking and *BDNF* secretion (Chen, Patel et al., 2004).

BDNF levels influence dopamine receptor expression (Guillin et al., 2007), and modulate GABAergic and serotonergic neurotransmitter systems (Angelucci et al., 2005). Further, there is evidence that *BDNF* reduces both the stimulation of dopamine release in the striatum and induction of dopamine-related behaviors in animals, thus the *BDNF Val* allele may be associated with lower dopamine activity in the brain (Narita, Aoki, Takagi, Yajima, & Suzuki, 2003). The *BDNF* protein is most prominent in the hippocampus, plays a role in LTP (Poo, 2001; Bath & Lee, 2006), and affects hippocampal dependent memory (Egan, Kojima et al., 2003; Hariri et al., 2003). *BDNF* is also expressed in the prefrontal cortex (Baquet, Gorski, & Jones, 2004).

BDNF and risk for schizophrenia.

Several research groups have shown that levels of *BDNF* are reduced in schizophrenia (Buckley, Pillai, Evans, Stirewalt, & Mahadik, 2007; Hashimoto et al., 2005; Vinogradov, et al., 2009). Consistent with this, some initial studies suggested that the *BDNF* gene might be a risk marker for schizophrenia (Hong et al., 2003; Neves-Pereira et al., 2005), especially in the presence of depressive symptoms (Schumacher et al., 2005). But, similar to *COMT*, studies finding an association between *BDNF Val66Met* and schizophrenia have been inconsistent with respect to the risk allele, with some suggesting that the *Met* allele is related to more severe psychotic symptoms and earlier age of onset (Numata, Ueno, Iga et al., 2007; Gourion et al., 2005; Han et al., 2008), while others indicated that the *Val* allele was associated with elevated risk of

schizophrenia (Rosa et al., 2006; Neves-Pereira et al., 2005). Nonetheless, to date, most studies demonstrate no effect of *BDNF Val66Met* on risk for schizophrenia in Caucasian (de Krom et al., 2005; Skibinska et al., 2004; Egan, Weinberger, et al., 2003; Jönsson et al., 2006) and Asian samples (Tan et al., 2005; Qian et al., 2007; Chang et al., 2009; Watanabe, Muratake, Kaneko, Nunokawa, & Someya, 2006; Tochigi et al., 2006). Recent meta-analyses support this conclusion of no or modest association between *BDNF Val66Met* and schizophrenia (Qian et al., 2007; Jönsson et al., 2006; Xu, St. Clair, Ott, Feng, & He, 2007; Kanazawa, Glatt, Kia-Keating, Yoneda, & Tsuang, 2007).

BDNF and Cognition

Several studies have found an association of the *BDNF Val66Met* polymorphism with regional brain volume and cognition, and the results are highly consistent in showing more deficits in *Met* carriers who have lower levels of *BDNF*. Among healthy adults, *BDNF Met*/*Met* homozygotes show more verbal recall errors, a slowed P300 ERP during the oddball task, with corresponding alterations in hippocampal and lateral prefrontal activation, and reduced hippocampal gray matter (Schofield, et al., 2009). Other studies of healthy participants have revealed that *Met* carriers show poorer performance on learning and memory tasks, abnormal regional cerebral blood flow (rCBF) in the hippocampus and other medial temporal regions when performing learning and memory tasks (Egan, Kojima et al., 2003; Hariri et al., 2003), as well as decreased volume in the hippocampus (Bueller et al., 2006: Chepenick et al., 2009; Pezawas et al., 2004; Szesko et al., 2005), dorsolateral prefrontal cortex (Pezawas et al., 2004), and the temporal and occipital lobes (Ho et al., 2006). A recent report on over 300 healthy adolescents showed that *BDNF Met* carriers manifested a significant reduction in total

lobar volume, which was on average 28.34 cm^3 smaller than in the *Val*/*Val* carriers (Toro et al., 2009). The effect of the *Val*66*Met* genotype was independent of age, and most pronounced in white matter volume of the temporal and frontal lobes (Toro et al., 2009).

Consistent with this, most studies of *BDNF* and cognition indicate that the *Met* allele is related to poorer verbal and/or spatial memory in both healthy participants and schizophrenia patients (Dempster et al., 2005; Ho et al., 2006; Tan et al., 2005; Hariri et al., 2003; Egan, Kojima et al., 2003). One recent study found poorer N-Back task performance (but not WCST performance) in schizophrenia patients carrying the *Met* allele (Rybakowski et al., 2006). As with healthy participants, among schizophrenia patients, *BDNF Met* allele carriers have significantly smaller temporal and hippocampal volumes (Ho et al., 2006) and greater longitudinal decreases in frontal gray matter volume, with increases in the volume in the lateral ventricles (Ho, Andreasen, Dawson, & Wassink, 2007). In contrast to the preponderance of data showing greater deficits in *BDNF Met* carriers, a report by Rosa and colleagues (2006) revealed no effect of *Val66Met* on prefrontal functioning (WCST and Trails B) in a family-based association study.

Epistatic Effects and Cognitive function

As described above, research has revealed that both *COMT Val108/158Met* and *BDNF Val66Met* are associated with cognitive functions in schizophrenia patients and other populations. In the case of *COMT*, the findings are mixed (Minzenberg et al., 2006; Leung, McClure, Siever et al., 2007; Ehlis et al., 2007; Galderisi et al., 2005; Goldberg et al., 2003; Bilder et al., 2002; Nolan et al., 2004; Woodward et al., 2007; Egan et al., 2001; Neuhaus et al., 2009; Ho et al., 2005; van Amelsvoort et al., 2008; Dennis et al.,

2010; Ho et al., 2005; Tsai et al., 2006; Stefanis et al., 2004; Smyrnis et al., 2007), whereas the *BDNF Met* allele appears to be consistently linked with nonoptimal functioning and brain volumetric reductions in both healthy and clinical populations (Schofield, et al., 2009; Egan, et al., 2003; Hariri et al., 2003; Bueller et al., 2006: Chepenick et al., 2009; Pezawas et al., 2004; Szesko et al., 2005; Ho et al., 2006; Toro et al., 2009; Dempster et al., 2005; Ho et al., 2006; Tan et al., 2005; Hariri et al., 2003; Egan, Kojima et al., 2003). This has prompted investigators to consider the potential role of interactions among genes that influence the phenotypic expression of psychotic disorders (Dickinson & Elvevåg, 2009).

All genes have the potential for both additive and interactive effects. The term epistasis is used to refer to the interaction among genes. Epistasis takes place when the effects of one gene are modified by one or several other genes (i.e., modifier genes). Given that no single genetic variant acts in isolation, it has been argued that greater progress is likely to be achieved through exploration of epistatic effects, and researchers have begun to do just this. Not only do gene-gene interactions likely confer vulnerability and impact the expression of cognitive endophenotypes (and other intermediate stages), but epistatic interactions can also enhance or minimize the effects of a single gene. As an example, Nicodemus et al. (2007) demonstrated that *COMT* modulated several other polymorphisms (e.g., RGS4, G72, GRM3, DISC1) in conferring risk for schizophrenia (statistical epistasis), many of which demonstrated no effect on risk alone.

With respect to cognitive functions, other genetic variants related to dopamine regulation, including DAT 3'UTR (Prata et al., 2009), may have interactive effects with *COMT* on cognitive function and brain activation. For example, Prata et al. (2009)

reported that both schizophrenia patients and healthy controls demonstrated increased activation in the left supramarginal gyrus (inferior parietal lobe) when they were homozygous *Met* on the *COMT* variant and also carried the 9-repeat DAT allele. But this did not hold for those with the 10/10-repeat DAT allele. In *COMT* homozygous *Val* individuals, it was the 10/10-repeat genotype that showed greater left supramarginal gyrus activation over the 9-repeat DAT allele. This study highlights the utility in investigating epistatic effects between genes that regulate complementary biological processes (e.g., dopamine regulation). Similarly, Meyer-Lindenberg et al. (2006) also reported *COMT* haplotypic interaction between the *Val108/158Met* polymorphism, P2 promoter (rs2097603), and a SNP in the 3'region (rs165599) in determining prefrontal inefficiency during a working memory task.

It is possible that *COMT* and *BDNF* have additive or epistatic effects on cognitive performance. To date, however, only two studies have examined the joint effects of these candidate genes on cognitive performance. One, a study of schizophrenia patients by Han and colleagues (2008) tested the hypothesis that the *COMT-BDNF* gene interaction would be related to symptoms and executive function in schizophrenia. This hypothesis was based on previous findings from this research group that the *Met* allele of *COMT Val108/158Met* and the *Met* allele of *BDNF Val*66*Met* were associated with attentional deficit and more severe delusions in patients, which is assumed to be due to greater tonic dopamine activity in the prefrontal cortex. Participants were 96 schizophrenia patients who were administered the Stroop color word test and trail-making test B as measures of executive function. Consistent with prediction, there was a significant interaction, such that patients who were both *BDNF Met*/*Met* and *COMT*

Met/*Met* carriers had the highest scores on delusions and the poorest performance on word reading of the Stroop test, and longer trail-making test time, compared with the other three genotype combinations. The authors concluded that patients with the *COMT Met*/*Met* x *BDNF Met*/*Met* genotype have more delusional symptoms and poorer cognitive flexibility, when compared with the other three genotype combinations, because this particular combination is presumed to be associated with the highest level of brain dopamine activity. In other words, they argue that those who are *Met* carriers on both *BDNF* and *COMT* have dopamine activity that is beyond the optimal level on the inverted-U. It is noteworthy, however, that this study did not directly examine verbal memory functions, which have shown the most direct association with brain dopamine activity (Vijayraghavan,et al., 2007).

In another recent report concerned with cognitive performance in healthy participants, Nagel et al. (2009) examined the relation of *COMT* and *BDNF* genotype with cognitive performance in younger (mean age = 25) and older (mean age = 65) healthy adults. They administered two tasks (Wisconsin Card Sorting and a spatial working memory task), and found that the relation of *COMT* genotype with cognitive performance was more pronounced in the older sample, and was modulated by *BDNF* genotype. Specifically, in the older sample, *COMT Val* homozygotes showed more WCST perseverative errors and longer response times on both tasks if they were also *BDNF Met* carriers. In interpreting their findings, the authors also note the evidence of an inverted U-shaped relation linking dopaminergic neuromodulation in PFC to cognitive performance. However, they suggest that the normative decline in dopamine activity may be more pronounced in elderly adults who are *COMT Val* carriers, thus depressing their

executive functions. Further, they interpret the finding that this effect is amplified for those with the *BDNF Met* allele to indicate that the combination of lower dopamine levels in *COMT Val* carriers with the impaired frontal and hippocampal function of *BDNF Met* carriers leads to the greatest performance deficits.

In summary, there is consistent support for poorer cognitive performance and reduced brain volume in both healthy samples and psychotic patients with the *BDNF Met* allele. The findings on *COMT* and cognitive performance are less consistent, however, and this has been hypothesized to be due, in part, to interactions with other genes. To date, only two studies have examined the interactive effect of *COMT* and *BDNF* on cognitive performance, and only one of these included a clinical sample. Yet, it appears that our understanding of the genetic determinants of cognitive deficits in schizophrenia spectrum disorders will be enhanced by studies of epistasis.

Goals of the Present Study

In the present study, the independent, additive and interactive effects of the *COMT* and *BDNF* genotypes are examined for their relation with cognitive function in the schizophrenia spectrum. Specifically, the relation between these genes and verbal memory function are examined, as previous research indicates that verbal memory is most sensitive to varying levels of dopamine activity (Vijayraghavan, et al., 2007). Evidence suggests that genetic factors confer a generalized risk for psychotic disorder, rather than a specific risk for schizophrenia (Tienari et al., 2003; Cannon et al., 2003). Therefore, the present study includes a broader sample of schizophrenia spectrum disorders, with both young patients with SPD, and older patients who met clinical criteria for schizophrenia, schizoaffective disorder, or psychosis not otherwise specified. There

are several advantages to a focus on the broader spectrum, including the lower exposure to psychotropic medications in schizotypal participants.

Drawing on past findings and theories implicating heightened dopamine activity in schizophrenia, this study tests the hypothesis that there is an interactive effect of *COMT* and *BDNF* on verbal memory performance in participants with schizophrenia spectrum disorders. Schizophrenia spectrum patients with both the *COMT* and *BDNF* *Met*/*Met* genotypes are predicted to show the most impaired performance, compared to the other genotypic combinations.

Method

Sample

Participants (N = 166) were drawn from two study sites. A sample of adolescents diagnosed with SPD, as well as age-matched normal and psychiatric comparison groups were from the Adolescent Development program at Emory University. In addition, the present study includes a sample of adult patients diagnosed with schizophrenia, schizoaffective disorder, and psychosis not otherwise specified, as well as their biological relatives, and matched controls from Grady Memorial Hospital, an affiliate of the Emory University School of Medicine.

Adolescent Development Program. A total of 130 adolescents were enrolled in the Emory University Adolescent Development Project. The present study sample includes the 61 participants (54.1% male) for whom genetic and cognitive data were available. There were no significant differences in cognitive performance between those with and without available genetic data. Diagnostic sample sizes are: SPD N = 15, normal control (NC) N = 24 and other psychiatric disorder (OPD) N = 22. Some participants in the

sample (N = 25) were relatives. There were no relatives within the SPD group. The sample ranged in age from 11-18 (M = 14.4; SD = 1.9) and included three main racial groups: white/Caucasian (52.5%), black/African American (41.0%), and Asian American (4.9%). Approximately two percent of the sample fell into the ethnic category labeled "other." Exclusion criteria were the presence of a neurological disorder, mental retardation, an Axis I disorder, or current substance abuse/addiction. A subgroup (N = 3) of individuals diagnosed with SPD was on one or more psychotropic medications.

ARIS Project. There were a total of 191 participants in the Associations Among Risk Indicators in Schizophrenia, second wave (ARIS-II) project, which investigated risk markers for schizophrenia among patients admitted to Grady Health System. Genetic and cognitive data were available for 105 participants (49.5% male). There was a significant difference between participants with and without genetic data on LM I performance (t = -2.608, df = 186, p = 0.010). No other memory measures were significantly different between included and excluded participants. The sample ranged in age from 18-73 (M = 36.4; SD = 12.7). The sample is comprised of two primary racial groups: black/African American (87.6 %) and white/Caucasian (12.4%). Participants fell into 3 diagnostic groups: psychotic patients (i.e., schizophrenia, schizoaffective disorder, psychosis NOS) N = 45, normal control (NC) N = 31 and a sample of first degree biological relatives of the patients (BR) N = 29.

Verbal Memory Tasks

Two subtests of the Wechsler Memory Scale, third edition (WMS-III; Wechsler, 1997), measuring learning, verbal memory, and working memory were administered to all participants. These subtests were selected because of their demonstrated ability to

differentiate between individuals with schizophrenia spectrum disorders and normal controls.

Logical Memory I and II. The Logical Memory subtests have an immediate and delayed component. Initially, participants are asked to retell two orally presented short-stories from memory. The second story is presented to them twice. Following a time elapse of 15 to 25 minutes, participants retell both stories presented initially to assess delayed recall. Logical memory I (LM I) is assumed to be a measure of immediate verbal memory. Logical memory II (LM II) assesses delayed verbal memory (Wechsler, 1997). The test yields two scores: a total recall score and a thematic recall score. The scores are computed by summing the total number of story and thematic elements recalled.

Letter Number Sequencing. Participants are presented with a string of alternating letters and numbers which gradually increase in length. They must repeat the numbers first after putting numbers in ascending order followed by the letters in alphabetical order. Letter-Number Sequencing (LNS) is thought to assess verbal working memory, the ability to remember and manipulate information presented orally (Wechsler, 1997). The test yields a score that reflects the total number of correctly recalled letters and numbers in the proper sequence. The scores are computed by summing the total number of correct items.

Procedures

The Adolescent Development Program recruited SPD participants through clinician referral, as well as announcements aimed at the parents of children with adjustment problems. Specifically, the announcement consisted of a lay description of key diagnostic criteria present in SPD. As expected, the announcement elicited responses

from parents whose children manifested a range of problems: those who met criteria for SPD as well as other Axis II disorders. Healthy control participants were recruited primarily through the Emory University based registry of children and adolescents in the Atlanta area. All prospective participants underwent telephone screening interviews, and those who met study criteria were scheduled for a research assessment. Following a telephone-screening interview, individuals who met criteria for study inclusion were invited for an initial four-hour research assessment. Informed consent was obtained from parents and assent was obtained from children.

All participants in the present study underwent a structured diagnostic interview that was conducted by a trained graduate-level clinician. Each assessment included the Structured Interview for DSM-IV Personality Disorders (SIDP-IV; Pfohl, Blum, & Zimmerman, 1997). Positive, negative, and disorganized symptom ratings were obtained by administering the Structured Interview for Prodromal Syndromes (SIPS; McGlashan et al., 2001). The Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) was administered to assess for Axis I psychopathology (SCID; First, Spitzer, Gibbon, & Williams, 1998). A saliva sample was taken at the conclusion of the assessment for DNA extraction.

All assessments were videotaped. Interviewers were trained in the administration of the procedures to meet a minimum Cohen's Kappa criterion of reliability of 0.85 for diagnoses with the SCID and SIDP-IV. In addition, research staff, including a licensed clinical psychologist and psychiatrist, reviewed videotaped interviews as well as other materials to establish consensus diagnosis.

The ARIS project recruited patients through clinician-referral at Grady Health System. Patients were invited to participate in the study and written informed consent was obtained. A trained examiner administered a research assessment including the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) and the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID; First et al., 1998). During the assessment procedure, patients were invited to provide research personnel with the name and telephone number of a first-degree relative that might be interested in participating in the study. Unaffected biological relatives were invited for study participation after their contact information was released by the respective patient. The normal comparison group was recruited from several sources, including an urban shopping center located in close proximity to the community mental health center, an ambulatory internal medicine clinic, and word of mouth from other control participants. Unaffected relatives and control participants were required to give informed consent prior to study participation. Each assessment included a battery of measures, and a saliva sample was taken at the conclusion of the assessment for DNA extraction.

Interviews for the ARIS project were conducted by a single, Ph.D. level interviewer who was trained in the administration of the procedures for SCID diagnosis. In addition, a psychiatrist reviewed the interview results, as well as other materials, to establish consensus diagnosis. Assessments conducted on the ARIS sample were not videotaped.

DNA Collection and Extraction

Saliva samples were collected from each participant using Oragene DNA Self-Collection kits from DNAGenotek (cat. no. OG-100). Participants deposited their saliva

into an Oragene solution inside the kit designed to preserve DNA. A proprietary buffer, rapidly sterilized the DNA and it was then stabilized within the buccal cells that shed and accumulate in saliva.

The Pure Link genomic DNA mini-kit (Invitrogen, cat. No. K1820-01) was used to extract DNA from 800µl of saliva collected in the Oragene kit. Between 80µl and 100µl of DNA was collected. DNA was then quantified at the Emory Center for Medical Genomics using pico-green. The DNA was then diluted to a working concentration of 1ng/µl and plated, using the Biomek FX, onto a 384-well microplate. For each sample, 5µl of working DNA was added to an individual well (5ng total) and allowed to dry down overnight. Negative controls and duplicates were incorporated into the DNA plate and the sample order was documented on an excel spreadsheet. The following day, 5µl of assay mix was added to each DNA well on the 384-well plate. This was done using the Biomek FX. The assay mix contained Universal PCR Master Mix no amperase UNG, (Applied Biosystems cat. no. 4326614), SNP genotyping assay (specific to each SNP, Applied Biosystems), and dH20. Real time polymerase chain reaction (PCR) was performed using the Taqman 7900HT and analyzed using the Sequence Detection Systems (SDS) Automation Controller software, version 2.3 from Applied Biosystems. Genotypes were acquired using the allelic discrimination program (within SDS, version 2.3) for samples with quality values at 95% or greater (call rate). The absolute quantification multi-component plots were used to make manual calls for the genotypes as needed. Because of the limited number of samples genotyping was repeated twice for accuracy. The genotypes from both experiments were compared using a quality check program. The duplicates concordant rate is ≥98%. Any discordant data were reanalyzed

using the real time PCR data. When the reaction signal was not robust, genotypes were considered indeterminable.

Table 3 – *COMT* genotype frequencies by diagnostic group

Table 4 – *BDNF* genotype frequencies by diagnostic group

Results

Data Analyses

Chi^2, Multiple Regression (MR), and Generalized Estimating Equation (GEE) procedures were conducted using SPSS 17. A description of how each set of analyses were conducted is presented below.

Chi^2 analyses were conducted using the Crosstabs function to compare genotypic frequencies across and within groups.

Multiple Regression analyses were used to test the proportion of variance in the dependent, verbal memory measures accounted for by each genetic variant as well as the interaction. (Similar analytic procedures were used by Han and colleagues (2008) who found an interaction between *COMT* and *BDNF* genes in relation to cognitive performance.) Each genetic variant was dummy coded (*COMT*: *Val*/*Val* = 1; *Val*/*Met* = 2; *Met*/*Met* = 3; *BDNF*: Val/Val = 1; *Val*/*Met* = 2; *Met*/*Met* = 3; *BDNF Met* carriers: 1=*Val*/*Val*; 2=*Met* carriers), and analyses were conducted entering the two genetic variants as predictors in one block, to test for main effects, then entering the interaction term in the subsequent block. Each dependent measure was ran first without covariates (with the exception of self-reported race when ethnicity differed within the population) and then with covariates.

The current sample also included non-schizophrenia spectrum individuals comprised of biological relatives (and healthy control participants). Data derived from related individuals are "clustered" or potentially correlated, while data derived from non-related individuals are uncorrelated (Williams, 2000). In addition, data collected at each recruitment site are expected to be correlated with other data collected at the same site. To address these issues, GEE (exchangeable working correlation matrix) was used to investigate the association between cognitive performance and genotype within families at the two recruitment sites. GEE was employed to account for correlated observations (or observations clustered within sampling units) (Norton, Bieler, Ennett, & Zarkin, 1996) that often result in underestimated regression standard errors and increased Type I error (Norton et al., 1996). The GEE-exchangeable method produces unbiased regression parameters by applying a simple correction that accounts for the within-cluster correlation and provides robust standard error estimates. For the current analyses, a robust estimator was specified for the covariance matrix and the structure of the working correlation matrix was exchangeable. The distribution specified was normal and analyses were completed first with the *Identity* link function (i.e., the dependent variable is not transformed) and then with the *Log* link function (i.e., log transformation of the dependent variable). Covariates were entered in the same manner discussed above with the exception of recruitment site which is entered as a subject variable in the current GEE analyses. In addition, independent families were entered as a subject variable and each person's position within a family (arbitrarily assigned) was entered as the within subject variable.

Preliminary Analyses of Distributions

The combined sample of 166 participants with data on at least one cognitive measure (LM I, LM II, or LNS) and one genetic variant (*COMT Val108/158Met* and/or *BDNF Val66Met*) was drawn from the original sample of 311 participants. To optimize the use of available data, the pairwise deletion method was used. Thus, the number of participants varied by analysis, and the degrees of freedom (*df*) for each analysis are presented. In addition, it should be noted that all three cognitive measures were significantly intercorrelated (LM I and LNS: $r = 0.485$, $p = .000$; LM I and LM II: $r = 0.901$, $p \leq 0.001$; LNS and LM II: $r = 0.519$, $p \leq 0.001$).

Preliminary exploration of the distributions of the dependent variables for the overall study sample ($N = 166$) revealed non-normally distributed data using the Kolmogorov-Smirnov (KS) test for LNS ($Z = 1.471$, $p = 0.026$) and LM II ($Z = 1.388$, $p = 0.042$), however LM I performance was normally distributed ($Z = 1.137$, $p = 0.151$).

Outliers were examined. There were no outliers more than 3 standard deviations above or below the mean for any measure. Logarithmic transformations were conducted; but did not normalize the data, and instead produced more deviant distributions ($p \leq 0.001$ for both measures). In an attempt to normalize the data, outliers were examined at 2.5 standard deviations above/below the mean. There was 1 outlier on LNS. After removal of this outlier, the KS test remained statistically significant. There were a total of 8 outliers at 2 standard deviations across all three measures. Four individuals were removed from LM I analyses, three from LNS analyses, and five from LM II analyses. It should be noted that 4 participants scored 2 standard deviations above the mean on more than one measure. After removing these outliers the distribution of all memory measures approximated a normal distribution (Figures 3, 4, and 5), but the KS test remained at

trend level for LM I (Z = 1.307, p = 0.066), and continued to be significant for LNS (Z = 1.601, p = 0.012) and LM II (Z = 1.583, p = 0.013). After removing outliers at 2 standard deviations greater than the mean, logarithmic transformations were performed to normalize LNS and LM II data, but these procedures only made the distributions more deviant ($p \leq 0.001$ for both measures).

Further examination of data within Caucasian (CAU; N = 42) and African American (AA; N = 116) participants revealed that the data within these subgroups were normally distributed for LM I (CAU: Z = 1.176, p = 0.126; AA: Z = 1.180, p = 0.123), LNS (CAU: Z = 0.882, p = 0.419; AA: Z = 1.283, p = 0.074), and LM II (CAU: Z = 1.006, p = 0.264; AA: Z = 1.267, p = 0.080). Please note that the remaining individuals not included in the dichotomous race analyses fell into the Asian (N = 3) and other (N = 1) groups. In summary, a total of 8 subjects with outlying scores on one of the 3 memory measures were excluded from one or more of the analyses.

Test of potential covariates

Self-reported race and recruitment site were examined for entry as covariates. There was a significant difference between AA and CAU participants, such that CAU subjects scored higher (LNS, t (143) = 4.06, $p < 0.001$; LM I, t (143) = 4.37, $p < 0.001$; LM II, t (143) = 4.23, p = 0.001) on all measures. There was also a significant difference between the Grady and Emory recruitment sites, such that participants from the Emory site scored higher on all measures (LNS, t (147) = 4.56, $p < 0.001$; LM I, t (147) = 5.08, $p < 0.001$; LM II, t (147) = 3.43, $p \leq 0.001$). The relation between self-reported race and recruitment site was also examined. These variables were significantly intercorrelated, but only moderately (r = 0.304, $p \leq 0.001$), therefore both were used as covariates.

Age was investigated as a potential covariate. Age was significantly correlated with performance on LM I (r = -0.204, p = 0.005), and LNS (r = -0.262, $p \leq 0.001$), but was not correlated with LM II performance (r = -0.039, p = 0.313). It should be noted that all dependent measures were significantly intercorrelated (LM I and LM II: r = 0.901, $p \leq 0.001$; LM I and LNS: r = 0.485, $p \leq 0.001$; LNS and LM II: r = 0.519, $p \leq$ 0.001). Given this, age was entered as a covariate for all dependent measures.

Sex was investigated for entry as a covariate in the current study. Performance was not significantly different between male and female participants LM I (t = -0.481, p = 0.631), LM II (t = -1.375, p = 0.171), or LNS (t = -0.233, p = 0.816). Given the difference in memory performance between recruitment site, the sample was split by recruitment site, there were no significant sex difference in LM I (Emory: t = -0.048, p = 0.962; Grady: t = -0.912, p = 0.364), LNS (Emory: t = 0.223, p = 0.824; Grady: t = -0.0653, p = 0.515), and LM II at the Emory site (t = -0.048, p = 0.962) but there was a trend for a sex difference between male and female participants at the Grady site on LM II (t = -1.942, p = 0.055). Sex differences were also investigated by race because of the significant ethnic differences in cognitive performance in our sample. There were no significant sex differences in LM I (CAU: -0.338, p = 0.737; AA: -0.572, p = 0.568), LM II (CAU: -0.787, p = 0.436; AA: -1.515, p = 0.132), LNS (CAU: .225, p = 0.823; AA: -0.553, p = 0.582).

Psychotropic medications in the schizophrenia spectrum subjects were examined for entry as statistical covariates in regression analyses. Antipsychotic use (N = 19) was associated with performance on LM I (t (70) = 2.89, p = 0.005), LM II (t (70) = 2.83, p = 0.006), and LNS (t (70) = 2.50, p = 0.02) such that those on medication scored

significantly below those not on medication. Mood stabilizers, stimulant, antidepressant, and anxiolytic medications did not demonstrate significant associations with any verbal memory measures. Antipsychotic medication use, coded 0 (none) or 1 (present), was entered as a covariate for analyses of all dependent measures.

For each dependent measure, analyses were completed 1) without covariates (with the exception of self-reported race that was entered in analyses of samples with heterogeneous ethnicity to minimize potential effects of population stratification), and 2) with self-reported race, recruitment site, age, sex, age X sex, and antipsychotic medication entered, and 3) with self-reported race, recruitment site, age^2, sex, and age^2 X sex, and antipsychotic medication to control for potential nonlinear effects of age and interactive effects of age and sex.

Diagnostic group differences in performance

Mean scores for the three dependent measures, covarying for race, are presented in Figures 6, 7, and 8. Using the General Linear Model (GLM), Multivariate, with race as a covariate, diagnostic group membership (SPD, psychotic patients, biological relatives, OPD, ARIS controls, ADP controls) was examined for its relation with performance and was significantly associated with all of the dependent measures (LNS: F (5,156) = 4.751, $p < 0.001$; LM I: F (5,155) = 5.568, $p < 0.001$; LM II, F (5,154) = 5.501, $p < 0.001$). GLM Multivariate contrasts (using the deviation method) comparing diagnostic groups revealed that the patients with a psychotic disorder (difference = -1.715, SE = 0.42, $p < 0.001$) scored below the mean of the other groups on the LNS, whereas those in the OPD group (difference = 1.416, SE = 0.55, $p < 0.01$) scored higher. For LM I, diagnostic group comparisons showed that the patients with psychotic

disorders (difference = -2.163, *SE* = 0.433, $p < 0.001$) scored below the mean of the other groups, whereas those in the ADP control (difference = 1.225, *SE* = 0.56, $p < 0.029$) group scored higher than other groups on LM I. Finally, on the LM II, diagnostic group comparisons showed that patients with a psychotic disorder (difference = -1.888, *SE* = 0.42, $p < 0.001$) scored below the mean while their biological relatives scored above the mean (difference = 1.246, *SE*= 0.481, $p < 0.01$) of the other groups. No other group comparisons reached significance.

When diagnostic groups were compared within site, controlling for race, there were no significant diagnostic group differences for the Emory site in LM I, LM II or LNS, although the trends were toward lower performance in the SPD group. For the Grady site, however, there were significant diagnostic group differences on all measures [LM I, (F (2,101) = 8.029, $p < 0.01$), LM II (F (2,100) = 13.231, $p < 0.001$), and LNS (F (2,100) = 3.182, $p < 0.05$)], with the psychotic disorders group scoring significantly lower on LM I (difference = -1.462, *SE* = 0.40, $p < 0.001$), LM II (difference = -1.677, *SE* = 0.34, $p < 0.001$), and LNS (difference = -0.993, *SE* = 0.39, $p < 0.02$). In addition, on LM II (difference = 1.332, *SE* = 0.39, $p < 0.01$), the biological relatives of the patients scored higher than the psychotic patients and controls. No other comparisons reached significance.

Quality Control Analyses for Genotyping

Allele frequencies from the current sample were compared to frequencies presented in the HAPMAP for different ethnicities (Table 5). As stated in the above section describing *DNA Collection and Extraction*, duplicate genotyping data was used to evaluate genotype concordance/discordance (concordance $\geq 98\%$). Allele frequencies

were also examined in the current sample to determine if they conformed to Hardy-Weinberg expectation (HWE) that is, to determine if allele frequencies were constant across generations and not effected by mutation, natural selection, migration, or assortative mating. Most human populations conform to HWE, and thus, deviations from HWE often represent genotyping error or the presence of population stratification (Wigginton, Cutler, & Abecasis, 2005). Both *COMT Val*108/158*Met* variant and *BDNF Val*66*Met* conformed to HWE.

Genotype frequencies

Genotype frequencies differed between racial subgroups for *COMT* (χ^2= 22.950, *df*= 2; $p \leq 0.001$), with a greater proportion of AA participants than CAU participants with the *Val*/*Val* genotype (57% vs. 17.4%). Analyses were therefore conducted separately by racial group, as well as controlling for race, to minimize bias due to population stratification. There were no differences in genotype frequencies of *BDNF* between racial groups (χ^2= 0.684, *df*= 1; p = 0.408).

Differences in genotype frequencies among psychiatric groups and controls are shown in Tables 6 and 7. Chi ^{2} test revealed that within the AA subgroup, there was a significant difference in the *COMT* genotype frequencies between SPD and ADP controls, such that 71.4% of AA individuals in the ADP group were *Val*/*Val* whereas, 0% of the SPD participants had the *Val*/*Val* genotype. There was also a trend level difference in the *COMT* genotype frequency between SPD participants and patients with a psychotic disorder (SPD = 0% *Val*/*Val* and psychosis = 57.1% *Val*/*Val*). There were no significant differences in *BDNF* genotype distributions in this subgroup. Within the CAU sample, there were no significant differences in the distribution of *COMT* or *BDNF* genotypes

among diagnostic groups. However, for some diagnostic comparisons, Chi^2 statistics could not be calculated due to small numbers of subjects.

The relations of genotype with performance

In the following, the results are presented first for individuals within the schizophrenia-spectrum. Schizophrenia-spectrum was operationalized as participants meeting diagnostic criteria for SPD or any psychotic disorder. Main and interactive effects of *COMT* and *BDNF* are presented within the schizophrenia-spectrum. All results presented for the schizophrenia-spectrum are presented within and across racial groups. Finally analyses are conducted using the entire sample, which includes individuals within the schizophrenia-spectrum, individuals with other psychiatric disorders, individuals with no psychiatric diagnosis, and relatives of patients diagnosed with SPD or a psychotic illness. Clinical (diagnosis, proportion on antipsychotic medication) and demographic (mean age, sex ratio) data for each diagnostic group are listed in Table 8.

Main Effects in the Schizophrenia-spectrum

Main effects of genotypes in relation to performance were first tested for the AA and CAU samples separately, and then combined. As noted, regression analyses were conducted first by entering genotype in block 1 (without covariates with the exception of self-reported race when necessary). In the second set of regression analyses for each dependent measure, covariates were entered in block 1and genotype was entered in block 2 to control for the effects of race, recruitment site, age, the potential effects of sex and the interaction between age and sex, and the effects antipsychotic medication on cognitive performance. The third set of regression analyses were completed replacing the age covariate with age^2 to control for potential nonlinear effects.

Relation of COMT with Verbal Memory Function

Multiple regression analyses were conducted in AA schizophrenia spectrum individuals (N = 43) with *COMT* genotype as the predictor and scores on the LM I and LM II and LNS scores as the dependent variables. Results are presented in Table 9. *COMT* genotype was not predictive of verbal memory performance in this subgroup (LM I: t (42) = -0.101, p = 0.920; LM II: t (42) = -0.255, p = 0.800; LNS: t (42) = -0.656, p = 0.516). Completing the analyses with covariates did not change the results (Table 9).

Regression analyses conducted in schizophrenia spectrum CAU participants (N=16) also revealed no significant association of *COMT* genotype and LM I (t (15) 0.198 p = 0.846) II (t (15) = -0.229, p = 0.822), or LNS (t (14) = -1.894, p = 0.081) performance. Entering covariates did not change results for LM I and II. LNS performance, however, was significant in this subgroup after entering covariates (t (14) = -4.670, p = 0.002) (Figure 9, Table 9). The result for LNS performance remained after the age^2 sequence of covariates was entered (t (14) = -3.192, p = 0.013).

In the total sample of schizophrenia-spectrum individuals (N = 60), regression analyses were conducted. Results indicated that *COMT* genotype was not a predictor of verbal memory performance (LM I: t (59) = -0.264, p = 0.793; LM II: t (59) = -0.079, p = 0.938; LNS: t (58) = -1.054, p = 0.296). The addition of covariates did not change the results (Table 9).

Relation of BDNF with Verbal Memory Function

There was a low frequency of *BDNF Met*-carriers within the schizophrenia-spectrum group when subdivided by race (AA: N = 1; CAU: N = 2) therefore, it was not possible to conduct separate analyses of the main effects of *BDNF* by race.

Regression analysis in the overall schizophrenia-spectrum (N = 50) revealed no significant effect of *BDNF* genotype with LM I (t (49) = 1.789, p = 0.080), II (t (49) = 1.866, p = 0.068), and LNS (t (48) = 1.781, p = 0.082). Entering covariates yielded no significant findings for LM I, II, or LNS (Table 10).

Additive and Interactive Effects in the Schizophrenia Spectrum

Regression analyses were conducted using *COMT* and *BDNF* genotype and the interaction term as the predictor variables, and cognitive scores as the dependent measures. All covariates were entered in block 1 in the same manner described above. *COMT* and *BDNF* genotype were entered in block 2, and the interaction term in the third block. In subsequent analyses, predictor variables (*COMT* and *BDNF*) were entered in separate blocks to determine incremental variance. Covariates were entered in the manner described above. Analyses were not conducted separately by race because of the low frequency of *BDNF Met*-carriers within each racial group. Results are presented in Tables 11-13.

Analyses of all schizophrenia-spectrum participants revealed no significant additive effects of *COMT* and *BDNF* on LM I, II or LNS. Adding covariates did not change the results for LM I or LM II, but there was an additive effect of COMT and BDNF when including linear (F (48) = 2.578, p = 0.023) and nonlinear (F (48) = 2.549, p = 0.024) covariates. The interaction between *COMT* and *BDNF* was not significant for any verbal memory measure, and including covariates in block 1 did not change the results. *BDNF* explained no significant additional variance over *COMT* for any memory measure. Results remained the same when covariates were added.

COMT and BDNF Effects in the Overall Sample

GEE was used to test the relation of *COMT* and *BDNF* genotypes with performance across the entire sample. In these analyses, *COMT*, *BDNF*, and the interaction term were entered as the predictor variables, and performance on the three verbal memory measures were the dependent variables. As stated above, covariates were entered in the same manner discussed above with the exception of recruitment site which is entered as a subject variable in the current GEE analyses. In addition, independent families were entered as a subject variable and each person's position within a family (arbitrarily assigned) was entered as the within subject variable. All GEE analyses included in this section were completed with the both the identity link and the log link as described above.

COMT, *BDNF*, or the interaction of *COMT* and *BDNF* were significant predictors of LM I, LM II, or LNS performance. Adding covariates did not change the results. Results were unchanged when the log link function was used (Table 14). However, it should be noted that for LM I and LM II the model did not converge when covariates were added with the logarithmic transformation was specified.

Sex-Specific Effects of COMT and BDNF on Verbal Memory Performances: Exploratory Analyses

Exploratory analyses investigating sex effects were conducted. Analyses using covariates followed the pattern described throughout the paper. All results can be found in Table 15.

GEE analyses revealed no sex-specific main effects of *COMT* or *BDNF* for male participants on LM I or LM II performance. However, there was a main effect of BDNF on LNS performance in men (*Wald* χ^2= 103150.976, $p \leq 0.001$). *Met* carriers

outperformed men with the *Val*/*Val* genotype on *BDNF*. It should be noted that *Met* carriers comprised only 12% of the male subgroup. This effect was no longer present when conducting covariate analyses. Results were unchanged when using the Log link function.

For female participants, however, there were no main effects of *COMT* on LM I or LM II performance. For LNS performance, *COMT* was a significant predictor (*Wald* χ^2= 113031.618, $p \leq 0.001$), such that *Val*/*Val* performed significantly lower than *Val*/*Met* individuals (Figure 10). There was no significant difference between *Val*/*Met* and *Met*/*Met* genotypes. The effect of *COMT* on LNS performance remained through all covariate analyses. *BDNF* was a significant predictor of LM I (*Wald* χ^2= 4.001, p = 0.045) and LNS (*Wald* χ^2= 3.640, p = 0.056) performance in women. The effect of the *BDNF* variant on LM I and LNS performance was not present in covariate analyses. There was no main effect of *BDNF* on LM II performance in women. Analyzing data using the Logarithmic transformation did not change results.

The interaction between *COMT* and *BDNF* on LM I (*Wald* χ^2= 14.640, p = 0.001), LM II (*Wald* χ^2= 17.804, $p \leq 0.001$), and LNS (*Wald* χ^2= 12.885, p = 0.002) performance in men was significant, and remained throughout all covariate analyses (Figure 11). The interaction term on LM I performance was statistically significant with the addition of covariates (linear: *Wald* χ^2= 70.353, $p \leq 0.001$; nonlinear: *Wald* χ^2= 70.050, $p \leq 0.001$) in women. Women also demonstrated a significant *COMT*/*BDNF* interaction on LM II (*Wald* χ^2= 21.919, $p \leq 0.001$) and LNS (*Wald* χ^2= 21.625, $p \leq 0.001$) performance, which remained with the addition of covariates (Figure 12).

The interaction between genotype and sex was tested. There were no interactive effects of *sex* and *COMT* on LM I, II, or LNS performance. Logarithmic transformations of the dependent variables did not change the results. The interaction of *sex* and *BDNF* could not be tested due to the low frequency of *Met* carriers within the female subgroup ($N = 3$).

Discussion

Studies of cognition and *COMT* and *BDNF* polymorphisms are mixed (Ehlis et al., 2007; Woodward et al., 2007; Ho et al., 2005; Amelsvoort et al., 2008), but there relation with dopamine neurocircuitry (Savitz et al., 2006; Goldman-Rakic et al., 2004) and prefrontal (Pezawas et al., 2004; Savitz et al., 2006), and medial temporal (Ho et al., 2006; Egan et al., 2003; Hariri et al., 2003) functions make them biologically relevant for investigating the additive and interactive effects of genetic variation on cognition. The literatures on *COMT* and *BDNF* in schizophrenia and other psychotic disorders are quite extensive (Ehlis et al., 2007; Galderisi et al., 2005; Goldberg et al., 2003; Bilder et al., 2002; Nolan et al., 2004; Woodward et al., 2007; Egan et al., 2001), yet there are only two published reports of *COMT* in patients diagnosed with SPD (Leung et al., 2007; Minzenberg et al., 2006) and no published reports on the *BDNF* gene in SPD participants. Additionally, there are only two studies describing the interactive effects on cognitive performance (Han et al., 2008; Nagel et al., 2009).

The current study aimed to clarify the relation between *COMT Val108/158Met* and *BDNF Val*66*Met* with verbal memory deficits in schizophrenia-spectrum disorders. Consistent with previous reports, patients diagnosed with a psychotic disorder manifested significant performance deficits on all of the verbal memory measures. Although the

participants with SPD showed a trend toward lower performance, the difference was not statistically significant. Also, consistent with recent meta-analyses, there were no diagnostic group differences in *COMT* or *BDNF* polymorphisms, and no main effects of either polymorphism on cognitive performance in the schizophrenia-spectrum group. Although the low frequency of *BDNF Met* carriers compromised power for detecting an interactive effect, the results did not indicate any trends. Thus, the findings of the current investigation did not support the hypothesized relationships. In secondary analyses, sex-specific effects of *COMT* and *BDNF* on verbal memory were investigated. These results suggest sex-specific effects and highlight the complex nature of genetic effects on cognition. However, cautious interpretation is warranted given the present study limitations.

Relation of COMT with Verbal Memory Performance

As noted above, in an attempt to understand the mixed findings in the *COMT* literature, researchers now point to the "inverted U" relation between dopamine and cognition, whereby too little or too much dopamine receptor stimulation in the prefrontal cortex (manipulated via dopamine agonists/antagonists or cognitive load) impairs working memory (Mattay et al., 2003; Vijayraghavan et al., 2007). More specifically, it is assumed that moderate levels of dopamine stimulation result in optimal cognitive performance through reductions in distractibility, but when stimulation is too low or too high, the result is cognitive impairment. The inverted U was not tested in the current sample as analyses showed no evidence of a nonlinear relationship between the *COMT Val108/158Met* or *BDNF Val66Met* polymorphism and cognition.

In healthy samples, there is some evidence that *Val*/*Val* individuals have the poorest performance on moderately difficult tasks, but this effect is not as consistent or pronounced in schizophrenia patients. In line with null findings of the link between *COMT* and cognition (Amelsvoort et al., 2008; Dennis et al., 2009; Ho et al., 2005; Tsai et al., 2003; Stefanis et al., 2004; Smyrnis et al., 2007), the current study also failed to find an independent effect of *COMT* on any verbal memory measure in schizophrenia-spectrum participants. When examining the data across the entire sample (i.e., schizophrenia-spectrum, healthy controls, biological relatives, and participants with other psychiatric disorders) *COMT* was not a significant predictor of verbal memory performance.

Relation of BDNF with Verbal Memory Performance

Multitudes of neurobiological and cognitive data consistently demonstrate that there is more consistent evidence of poorer verbal and working memory functions in schizophrenia patients and healthy controls who are *BDNF Met*-carriers (Dempster et a., 2005; Ho et al., 2006; Tan et al., 2005; Hariri et al., 2003; Egan et al., 2003; Rybakowski et a., 2006). Nonetheless, in the present study *BDNF* was not an independent predictor of cognitive performance for schizophrenia-spectrum participants. Again, however, it is important to note that the small number of *Met* carriers compromised statistical power for detecting such a relation. In line with the current study, Rosa and colleagues (2006) failed to find an effect of *BDNF Val*66*Met* on cognition in a family-based study. Yet, the study by Rosa et al. (2006) was an examination of prefrontal cognition (Trail-Making Test, Form B; WCST: perseverative errors and number of categories), rather than memory as in the current analysis.

When tested with the entire sample, *BDNF* was not a significant predictor of LM I, LM II, or LNS performance. Contrary to prediction from previous research, there was no effect of *BDNF Val66Met* on verbal memory performance. Again, the low frequency of *Met* carriers likely limited statistical power for detecting an effect. Based on the extant literature, *Met* carriers are estimated to comprise approximately 30% of the population, with only 4% manifesting the *Met*/*Met* genotype in individuals of European descent (Shimizu et al., 2004). In the present sample, the frequency was lower, with only 7.8% *Met* carriers. This may reflect some unique aspect of the sample (e.g., ethnicity: 71% African American), or may simply be a chance occurrence.

Additive and Interactive Effects on Verbal Memory Performance in the Schizophrenia Spectrum

There is great utility in the investigation of genes that regulate the same biological processes (e.g., dopamine regulation). As described above, only two studies to date have investigated the interactive effect of *COMT Val108/158Met* and *BDNF Val66Met* on cognitive performance (Nagel et al., 2009; Han et al., 2008), and only one of these studies investigated this effect in schizophrenia patients (Han et al., 2008). The study by Han and colleagues (2008) demonstrated a significant *COMT-BDNF* interaction. Specifically, individuals who were *Met* carriers on both *COMT* and *BDNF* were assumed to be characterized by dopamine activity that was beyond the optimal level on the inverted U, and thus had the poorest cognitive performance. Further, evidence of the inverted U was found in a healthy sample, but in this sample it was the *COMT Val*/*Val* genotype and *BDNF Met* carriers that were most impaired (Nagel et al., 2009). The current study failed to replicate the Han et al. (2008) findings, although the current investigation examined

verbal memory performance, which is postulated to be more directly linked to dopamine activity (Vijayraghavan et al., 2007).

Secondary Analyses of Sex Effects on Verbal Memory Performance

Exploratory analysis of sex differences revealed differential effects of *COMT Val108/158Met* and *BDNF Val66Met* on cognition in men and women. The *COMT* polymorphism was not a significant predictor of LM I, LM II or, LNS performance in men. Likewise, *COMT* was not a significant predictor of LM I or LM II performance in women. *COMT*, did however, predict LNS performance in the female subgroup, such that *Val/Val* performed lower than *Val/Met*. Thus, findings within the subgroup of women are consistent with prior reports showing poorer performance in *Val* allele carriers (Egan et al., 2001; Malhotra, Kestler et al., 2002; Rosa et al., 2004; Bilder, Volavka, Czobor et al., 2002; Aguilera, Barrantes-Vidal, Arias et al., 2008).

For the *BDNF* polymorphism, on the other hand, men with the *Val*/*Val* genotype had poorer performance than men who were *Met* carriers. In women, the *Val66Met* variant was a significant predictor of LM I and LNS performance.

As stated earlier, the interaction between *COMT Val108/158Met* and *BDNF Val66Met* was not significant for the overall sample. But when tested separately for men and women, the interaction between *COMT* and *BDNF* was significant. As illustrated in Figures 11 and 12 the *COMT-BDNF* interactive effects are reversed between the sexes. Taken together, this suggests the possibility that combining the data from the subpopulations of men and women may have obscured sex-specific interactive effects of the *COMT* and *BDNF* variants in the overall sample.

Results did not reveal a significant Sex X *COMT* interaction and the Sex X *BDNF* interaction could not be investigated due to the low number of Met Carriers in the female subgroup. Sex-specific effects have been reported in a study by Shifman and colleagues (2002) who examined the relation of another *COMT* SNP (rs165599) with risk for schizophrenia. Although the secondary sex-specific effects are intriguing, they are based on small sample sizes and must be interpreted with caution. Nonetheless, they highlight one of many factors that can moderate the relation of candidate genes with cognitive performance measures.

Genetic Factors related to Null Findings

Inherent complexities in the study of genes and behavior make null findings challenging to interpret, as multiple genes, more than can currently be included in any one study, presumably play a role in the complex relationship among *COMT*, *BDNF* and cognition. Genetic effects on cognitive processes can be both pleiotropic and polygenic. Further, gene-environment interactions and epigenetic processes are likely involved. All of these could affect cognition or moderate an effect through some other downstream functional change. In addition, linkage disequilibrium may contribute to mixed findings, particularly, in the *COMT* literature. For example, it is plausible that the *COMT Val108/158Met* polymorphism is in LD with some other genetic variant that affects cognition. For example, Shifman and colleagues (2002) reported that rs4633 is in LD with *Val108/158Met* in risk for schizophrenia.

Clinical Factors related to Null Findings

There are numerous potential confounding variables in studies of the relation between genes and cognition, especially in psychiatric populations. One challenge is the

effect of psychotropic medication. There is evidence that psychotropic medications, particularly antipsychotics, can have adverse effects on cognitive performance (Byerly, 2001). But estimating and covarying for these effects is challenging, because psychotropic medications are not administered at random. Rather, symptom severity typically determines both the likelihood of being prescribed medication and the dosage that is prescribed. In particular, among SPD participants, the subgroup on an antipsychotic is likely to have been the most impaired pretreatment. Further, there is rapidly accumulating evidence that genetic factors partially determine medication responses (Arranz & Leon, 2007).

Current Study Limitations

A chief limitation of the present study is the small sample size and the concomitant underrepresentation of *BDNF Met* carriers. This limited power for detecting both main and interactive genetic effects. The sample size also prevented the investigation of the inverted U effects of dopamine on cognition, as early analyses showed no evidence of nonlinear effects. In addition, the current study was conducted with a sample from two primary ethnicities, AA and CAU. The potential problem of population stratification was addressed by statistically controlling for self-reported race. There is no doubt that a more rigorous approach would have been to use ancestry informative markers (AIMS) to correct for spurious associations (population stratification) (Halder, Shriver, Thomas, Fernandez, & Frudakis, 2008; Epstein, Allen, Satten, 2007). Analyses using AIMS entail statistical association tests with random markers which are then used to adjust the statistical tests between candidate loci and

phenotypes. However, the number of genetic markers collected for the present study, and many others in the field, was insufficient for this approach.

The assumption guiding research on cognitive processes in schizophrenia-spectrum disorders is that cognitive deficits may 1) underlay risk for psychotic symptoms, and/or 2) be one of several manifestations of genetically-determined vulnerability. In addition, however, there are presumed to be adverse effects of *symptoms on cognitive performance*. Although studies of schizophrenia patients show that cognitive deficits often predate the onset of clinical symptomatology (Fuller, Nopoulos, Arndt, et al., 2002; Ang and Tan, 2004; Erlenmeyer-Kimling, Rock, Roberts, et al., 2000), cognitive performance has been shown to decline as symptoms become more severe (Bilder et al., 2000; Mohamed et al., 1999; Nieuwenstein et al., 2001; Aleman et al., 1999). Obviously, however, disentangling the bidirectional relation between symptoms and cognitive performance is a formidable task. Thus, differentiating genetically determined from symptom-induced cognitive deficits would entail a large sample, longitudinal study. In addition, IQ is a frequent covariate in the study of deficits in specific cognitive domains however; this data was not available across both study samples for the current study.

Future Directions

There are quite likely additional factors at play in the relationship between genes and cognition, such as developmental stage, hormones and a range of exogenous factors. For example, a recent report from our research group (Walder et al., 2010, in press) suggests an association between *COMT* and developmental changes in cortisol in high-risk youths. It is no longer surprising that psychotic symptoms are exacerbated by

stress—and the *BDNF* protein acts as a stress buffer, which is evident from the effects of antidepressant medication on *BDNF* in the hippocampus (Balu, Hoshaw, Malberg, Rosenzweig-Lipson, Schechter, Lucki, 2008; Lipska, Khaing, Weickert, Weinberger, 2001). Animal studies suggest that the clinical effectiveness of antidepressants is a function of the upregulation of the *BDNF* protein (Duman, 2002). Reductions in serum *BDNF* are thought to mediate the neurotoxic effects of stress on hippocampal plasticity (Duman, Malberg, & Thorne, 1999). Thus, it is possible that elevations in serum *BDNF* act as a buffer against psychotic symptoms. To date, few studies have directly investigated the relation between *BDNF* polymorphisms and cortisol regulation among psychiatric patients (Shalev, Lerer, Israel et al., 2009). Previous reports on the effects of *BDNF* in the hippocampus suggest an inverse association between serum *BDNF* and cortisol (Poo, 2001; Bath & Lee 2006).

In addition to neurobiological factors, genomic variation, other than SNPs, likely impact cognitive performance. One example is Copy Number Variants (CNVs). While beyond the scope of the current manuscript, these mutations result from large insertions, deletions (e.g., 22q11.2 DS), and translocations often affecting one or more genes (Walsh, McClellan, McCarthy, Addington, Pierce, Cooper et al., 2008) and may play a critical role in understanding risk and development for psychiatric disorders and their associated features (e.g., cognition).

More recently the field of psychiatric genetics has begun conducting genome-wide association studies (GWAS) to identify susceptibility genes for schizophrenia. GWAS studies genotype between 100,000 and one million SNPs in each participant to test for association between any number of the selected SNPs with the trait in question.

The use of GWAS for genetic discovery assumes that the genetic variation related to the illness (e.g., schizophrenia) is common in the population (Hall & Smoller, 2010). To date these studies have not yielded results that reach genome-wide significance for the *COMT* or *BDNF* variants (O'Donovan, Craddock, Norton, et al., 2008; Need, Ge, Weale, Maia, Feng, Heinzen et al., 2009; Sullivan, Lin, Tzeng, van den Oord, Perkins, Stroup, Wagner, lee, Wright, Zou, Liu, Downing, Lieberman, Close, 2008) The discovery of a finite number of "risk genes" for schizophrenia is a fast fading notion, as GWAS studies are demonstrating that the genetic mechanisms underlying risk for schizophrenia are likely polygenic and involve thousands of alleles of very small effect (The International Schizophrenia Consortium, 2009).

Studies must also continue to consider the role of cognitive impairment as a putative endophenotype for schizophrenia. The current study failed to provide support for the WMS verbal memory measures as useful endophenotypes as measured by some of the validity criterion listed above (i.e., intermediate performance in relatives). In addition, studies of cognition have not demonstrated a meditational effect of cognitive impairment between genetic variability and the schizophrenia illness.

Multiple factors influence the effects of genes on cognition and future studies should continue to investigate the multiple contributing factors to impaired cognition in psychosis. Studies indicate that the effects of *COMT* may extend beyond prefrontal functions (Harris et al., 2005; de Frias et al., 2004), but the literature on other cognitive functions is sparse and it is increasingly evident that future psychiatric genetic studies should begin exploring a broader range of cognitive functions.

Clinical Implications

Endophenotypic markers related to prodromal signs of illness, like post-pubertal cognitive decline, may help researchers and clinicians identify individuals at greatest risk for developing schizophrenia and other psychotic illness. Studies demonstrate that real-world functional impairment (social, academic, and occupational functioning) and problems with social functioning are associated with cognitive deficit (Green et al., 2004; Bowie et al., 2006; Bell et al., 2008; Brekke et al., 2007; Milev et al., 2005). From this research, it is unclear which risk marker is evident earlier. Nonetheless, using well-known and well-validated measures of verbal memory, as in the current study, that can be routinely administered will aid clinicians in early identification of at-risk individuals.

Research on the duration of untreated psychosis (DUP) repeatedly demonstrates the beneficial impact and better treatment outcome for individuals who are identified early compared to those that go without help (Drake et al., 2000; Johannessen et al., 2001; McGlashan, 2001). The use, then, of measures with the potential to identify adolescents in the schizophrenia prodrome are crucial to our understanding of the etiology of the disease.

Current literature on the efficacy of psychosocial treatments for schizophrenia is limited and to date, pharmacological agents, though problematic, have been the gold standard in treatments for schizophrenia. Studies in pharmacogenetics suggest differential treatment effects for *COMT* and *BDNF* polymorphisms. Specifically, *COMT Met*-carriers demonstrated significant improvement on attention and verbal fluency measures following 6 months of Clozapine treatment compared to *Val*/*Val* individuals (Woodward et al., 2007). Another study found that after antipsychotic treatment, individuals

homozygous for the *COMT Met* allele had improvements in working memory, whereas *COMT* homozygous *Val* individuals did not show this improvement (Weickert, Goldberg, Mishara et al., 2004).

Concluding Thoughts

Schizophrenia-spectrum disorders are illnesses with multiple etiologies and heterogeneous symptom profiles that arise from genes with differential effects. Genes, however, are only one avenue on the path of discovery toward new mechanisms in the pathogenesis of this debilitating illness.

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Table 1. DSM-IV Criteria for Schizophrenia

A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of the time during a 1-month period (or less if successfully treated):

(1) delusions

(2) hallucinations

(3) disorganized speech (e.g., frequent derailment or incoherence)

(4) grossly disorganized or catatonic behavior

(5) negative symptoms, i.e., affective flattening, alogia, or avolition

Note: Only Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

B. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure ot achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or tow or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective and Mood Disorder exclusion: Schizoaffective Disorder and Mood Disorder with Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. Relationship to a Pervasive Developmental Disorder: If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Classification of longitudinal course (can be applied only after at least 1 year has elapsed since the initial onset of active-phase symptoms):

Episodic With Interepisode Residual Symptoms (episodes are defined by the reemergence of prominent psychotic symptoms); also specify if: With Prominent Negative Symptoms

Episodic With No Interepisode Residual Symptoms

Continuous (prominent psychotic symptoms are present throughout the period of observation); also specify if: With Prominent Negative Symptoms

Single Episode In Partial Remission; also specify if: With Prominent Negative Symptoms

Single Episode in Full Remission

Other or Unspecified Pattern

Table 2. DSM-IV Criteria for Schizotypal Personality Disorder

A.	A pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behavior, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:
1	ideas of reference (excluding delusions of reference
2	odd beliefs or magical thinking that influences behavior and is inconsistent with subcultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy, or "sixth sense"; in children and adolescents, bizarre fantasies or preoccupations)
3	unusual perceptual experiences, including bodily illusions
4	odd thinking and speech (e.g., vague, circumstantial, metaphorical, overelaborate, or stereotyped)
5	suspiciousness or paranoid ideation
6	inappropriate or constricted affect
7	behavior or appearance that is odd, eccentric, or peculiar
8	lack of close friends or confidants other than first-degree relatives
9	excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self
B.	Does not occur exclusively during the course of Schizophrenia, a Mood Disorder with Psychotic Features, another Psychotic Disorder, or a Pervasive Developmental Disorder

Note: If criteria are met prior to the onset of Schizophrenia, add "Premorbid," e.g., "Schizotypal Personality Disorder (Premorbid)."

Table 3. COMT genotype by diagnostic group

	Cases (N=82)			Relatives (N=29)	Controls (N=54)	
	SPD (N=15)	Psychosis (N=45)	Other Disorders (N=22)		ADP (N=24)	ARIS (N=30)
Val/Val	3	22	7	17	10	16
Val/Met	9	16	10	7	11	13
Met/Met	3	7	5	5	3	1

Table 4. BDNF genotype by diagnostic group

	Cases (N=72)			Relatives (N=29)	Controls (N=53)	
	SPD (N=15)	Psychosis (N=35)	Other Disorders (N=24)		ADP (N=24)	ARIS (N=30)
Val/Val	12	34	20	25	21	25
Met-Cariers	3	1	2	------	3	4

Table 5. Genotype Frequencies (in Percent) in the current sample vs. HAPMAP

	COMT Val/Val	COMT Val/Met	COMT Met/Met	BDNF Val/Val	BDNF Val/Met	BDNF Met/Met
HAPMAP: African Ancestry	50	41.7	8.3	---	---	---
HAPMAP: European Ancestry	21.7	53.3	25	68.3	28.3	3.3
Current Study: African American	31.7	19.3	4.6	46.3	3.2	---
Current Study: Caucasian	8.3	25	14.6	39.6	5.2	---

Table 6. Diagnostic differences in distribution of COMT genotypes

African Americans		Control Participants	Psychosis	Other psychiatric disorders	Biological Relatives
	SPD	$\chi 2$= 8.663, p=.013	$\chi 2$= 4.803, p=.091	$\chi 2$= 1.851, p=.396	---
	Psychosis	$\chi 2$= 2.331, p=.312	---	---	$\chi 2$= 1.552, p=.460
Caucasian					
	SPD	$\chi 2$= 1.489, p=.475	$\chi 2$= 2.252, p=.324	$\chi 2$= .281, p=.869	---
	Psychosis	---	---	---	$\chi 2$= 1.867, p=.393

Table 7. Diagnostic differences in distribution of BDNF genotypes

African Americans		Control Participants	Psychosis	Other psychiatric disorders	Biological Relatives
	SPD	$\chi 2$= .697, p=.404	$\chi 2$= .933, p=.334	---------	---------
	Psychosis	$\chi 2$= 2.550, p=.110	---------	---------	$\chi 2$= .587, p=.444
Caucasian					
	SPD	$\chi 2$= .509, p=.476	$\chi 2$= 1.051, p=.305	$\chi 2$= .180, p=.671	---------
	Psychosis	---------	---------	---------	---------

Table 8. Clinical and Demographic Characteristics

	Schizophrenia-Spectrum (N=60)				Controls (N = 55)	
	SPD (N=15)	Psychosis (N=45)	OPD (N=22)	Relatives (N=29)	ADP (N=24)	ARIS (N=31)
Age, mean (SD)	14.47 (1.88)	30.09 (8.50)	14.27 (1.78)	44.00 (17.67)	14.42 (1.98)	38.29 (6.54)
% Male, n (%)	9 (60.0)	29 (64.4)	12 (54.5)	5 (17.2)	12 (50.0)	18 (58.1)
% CAU, n (%)	10 (66.7)	6 (13.3)	11 (50.0)	7 (24.1)	11 (45.8)	31 (100)
% AA, n (%)	4 (26.7)	39 (86.7)	8 (36.4)	22 (75.9)	13 (54.2)	-------
% Asian American, n (%)	1 (6.7)	-------	2 (9.1)	-------	-------	-------
% Other	-------	-------	1 (4.5)	-------	-------	-------
% Anxiolytics, n (%)	-------	3 (6.7)	-------	-------	1 (4.3)	
% Antipsychotics, n (%)	2 (14.3)	14 (31.1)	-------	-------	3 (13.0)	-------
% Antidepressants, n (%)	3 (21.4)	2 (4.4)	2 (11.1)	-------	2 (8.7)	-------
% Mood Stabilizer, n (%)	1 (7.1)	5 (11.1)	2 (11.1)	-------	-------	-------
% Stimulants, n (%)	5 (35.7)	-------	2 (11.1)	-------	2 (8.7)	-------
LM I, mean (SD)	7.60 (3.22)	4.80 (2.77)	8.68 (4.08)	7.31 (2.99)	8.75 (2.83)	6.64 (2.68)
LM II, mean (SD)	7.60 (3.22)	5.44 (2.72)	8.68 (4.08)	8.72 (2.72)	8.75 (2.83)	7.35 (2.81)
LNS, mean (SD)	7.73 (3.45)	5.44 (2.99)	9.00 (2.35)	7.34 (3.36)	8.29 (2.26)	6.68 (2.88)

(Psychosis Group Includes: schizophrenia N=33; schizoaffective N=11; psychosis NOS N=1)

Table 9. Main Effects of COMT on Cognitive Performance in the Schizophrenia-Spectrum

	AA SZ-spectrum (N =46)					CAU SZ-spectrum (N=16)					SZ-spectrum (N=60)				
Dependent Variable: LM I	R^2 Change	Sig F. Change	Beta	t	Sig	R^2 Change	Sig F. Change	Beta	t	Sig	R^2 Change	Sig F. Change	Beta	t	Sig
BLOCK 1	0.220	0.089				0.255	0.646				0.232	0.024			
Self-reported race													0.167	1.142	0.259
Recruitment Site			-0.240	-1.385	0.174			-0.390	-0.344	0.738			-0.340	-1.764	0.084
Age			-0.287	-0.565	0.576			0.506	0.407	0.692			0.023	0.057	0.954
Sex			-0.026	-0.052	0.959			0.136	0.161	0.875			0.101	0.300	0.765
Sex X Age			0.103	0.136	0.892			-0.542	-0.361	0.726			-0.204	-0.409	0.684
Antipsychotics			-0.222	-1.439	0.159			-0.339	-1.181	0.265			-0.247	-1.965	0.055
BLOCK 2	0.005	0.642				0.026	0.320				0.000	0.937			
Self-reported race													0.168	1.134	0.262
Recruitment Site			-0.269	-1.449	0.156			-0.854	-0.596	0.566			-0.337	-1.695	0.096
Age			-0.265	-0.515	0.610			0.584	0.451	0.663			0.017	0.041	0.967
Sex			-0.038	-0.075	0.941			0.040	0.045	0.965			0.100	0.294	0.770
Sex X Age			0.084	0.109	0.914			-0.183	-0.109	0.916			-0.197	-0.388	0.699
Antipsychotics			-0.205	-1.282	0.208			-0.329	-1.105	0.298			-0.249	-1.939	0.058
COMT			-0.077	-0.469	0.642			0.206	0.566	0.585			0.011	0.079	0.937

	AA SZ-spectrum (N =46)					CAU SZ-spectrum (N=16)					SZ-spectrum (N=60)				
Dependent Variable: LM II	R^2 Change	Sig F. Change	Beta	t	Sig	R^2 Change	Sig F. Change	Beta	t	Sig	R^2 Change	Sig F. Change	Beta	t	Sig
BLOCK 1	0.192	0.147				0.147	0.875				0.173	0.106			
Self-reported race													0.06	0.393	0.696
Recruitment Site			-0.279	-1.579	0.123			-0.626	-0.515	0.617			-0.304	-1.519	0.135
Age			-0.477	-0.924	0.362			-0.133	-0.100	0.922			0.061	0.149	0.882
Sex			-0.35	-0.678	0.502			-0.379	-0.419	0.684			0.056	0.159	0.874
Age X Sex			0.613	0.795	0.432			0.685	0.426	0.679			-0.061	-0.119	0.906
Antipsychotics			-0.207	-1.323	0.194			-0.363	-1.183	0.264			-0.28	-2.15	0.036
BLOCK 2	0.006	0.607				0.000	0.959				0	0.947			
Self-reported race													0.059	0.383	0.703
Recruitment Site			-0.311	-1.647	0.108			-0.673	-0.431	0.676			-0.307	-1.487	0.143
Age			-0.453	-0.865	0.393			-0.125	-0.089	0.931			0.066	0.158	0.875
Sex			-0.364	-0.696	0.491			-0.389	-0.400	0.698			0.057	0.16	0.873
Age X Sex			0.591	0.757	0.454			0.722	0.394	0.703			-0.067	-0.126	0.9
Antipsychotics			-0.189	-1.161	0.253			-0.362	-1.117	0.293			-0.279	-2.1	0.041
COMT			-0.087	-0.519	0.607			0.021	0.053	0.959			-0.009	-0.067	0.947

Dependent Variable: LNS	R^2 Change	Sig F. Change	Beta	t	Sig	R^2 Change	Sig F. Change	Beta	t	Sig	R^2 Change	Sig F. Change	Beta	t	Sig
BLOCK 1	0.135	0.349				0.234	0.736				0.142	0.219			
Self-reported race													0.017	0.109	0.914
Recruitment Site			0.001	0.007	0.995			1.823	1.419	0.19			-0.042	-0.209	0.836
Age			-0.26	-0.487	0.629			-0.363	-0.27	0.793			0.002	0.006	0.996
Sex			-0.016	-0.03	0.976			0.608	0.747	0.474			0.217	0.596	0.554
Age X Sex			-0.091	-0.114	0.91			-1.721	-1.065	0.314			-0.429	-0.799	0.428
Antipsychotics			-0.13	-0.801	0.428			0.061	0.201	0.845			-0.145	-1.084	0.283
BLOCK 2	0.025	0.304				0.56	0.002				0.036	0.142			
Self-reported race													-0.008	-0.052	0.959
Recruitment Site			-0.065	-0.338	0.737			3.768	4.597	0.002			-0.108	-0.531	0.598
Age			-0.211	-0.393	0.696			-0.607	-0.822	0.435			0.138	0.325	0.746
Sex			-0.044	-0.083	0.935			1.057	2.31	0.05			0.261	0.723	0.473
Age X Sex			-0.137	-0.171	0.865			-3.332	-3.499	0.008			-0.58	-1.073	0.289
Antipsychotics			-0.091	-0.548	0.587			0.016	0.098	0.925			-0.119	-0.891	0.377
COMT			-0.179	-1.042	0.304			-0.887	-4.67	0.002			-0.211	-1.492	0.142

Table 10. Main Effects of BDNF on Cognitive Performance in the Schizophrenia-Spectrum

	AA SZ-spectrum (N =35)					CAU SZ-spectrum (N=14)					SZ-spectrum (N=50)				
Dependent Variable: LM I	R^2 Change	Sig F. Change	Beta	t	Sig	R^2 Change	Sig F. Change	Beta	t	Sig	R^2 Change	Sig F. Change	Beta	t	Sig
BLOCK 1	0.257	0.107				0.247	0.752				0.260	0.035			
Self-reported race													0.172	1.106	0.275
Recruitment Site			-0.334	-1.632	0.114			-0.608	-0.515	0.621			-0.431	-1.952	0.057
Age			-0.424	-0.751	0.459			0.734	0.602	0.564			0.059	0.134	0.894
Sex			-0.314	-0.565	0.577			0.140	0.150	0.884			-0.006	-0.016	0.987
Age X Sex			0.442	0.520	0.607			-0.463	-0.297	0.774			-0.138	-0.251	0.803
Antipsychotics			-0.201	-1.161	0.255			-0.338	-1.051	0.324			-0.259	-1.887	0.066
BLOCK 2	0.046	0.187				0.195	0.162				0.005	0.582			
Self-reported race													0.150	0.933	0.356
Recruitment Site			-0.348	-1.721	0.096			-0.509	-0.467	0.655			-0.387	-1.631	0.110
Age			-0.170	-0.290	0.774			1.103	0.961	0.369			0.027	0.061	0.952
Sex			-0.164	-0.294	0.771			0.513	0.576	0.583			-0.005	-0.013	0.990
Age X Sex			0.129	0.148	0.883			-0.788	-0.543	0.604			-0.119	-0.215	0.831
Antipsychotics			-0.249	-1.428	0.164			-0.213	-0.694	0.510			-0.247	-1.764	0.085
BDNF			-0.230	-1.353	0.187			0.500	1.563	0.162			0.080	0.554	0.582

Dependent Variable: LM II	R^2 Change	Sig F. Change	Beta	t	Sig	R^2 Change	Sig F. Change	Beta	t	Sig	R^2 Change	Sig F. Change	Beta	t	Sig
BLOCK 1	0.226	0.168				0.169	0.884				0.220	0.084			
Self-reported race													0.112	0.700	0.487
Recruitment Site			-0.394	-1.887	0.069			-0.355	-0.286	0.782			-0.402	-1.772	0.083
Age			-0.492	-0.854	0.400			-0.475	-0.371	0.720			-0.105	-0.234	0.816
Sex			-0.472	-0.831	0.413			-0.418	-0.426	0.681			-0.077	-0.212	0.833
Age X Sex			0.781	0.901	0.375			0.674	0.411	0.692			0.172	0.305	0.762
Antipsychotics			-0.162	-0.917	0.367			-0.380	-1.126	0.293			-0.251	-1.783	0.082
BLOCK 2	0.027	0.322				0.240	0.136				0.013	0.403			
Self-reported race													0.079	0.477	0.636
Recruitment Site			-0.405	-1.936	0.063			-0.245	-0.218	0.833			-0.332	-1.373	0.177
Age			-0.297	-0.488	0.629			-0.067	-0.057	0.956			-0.154	-0.339	0.736
Sex			-0.357	-0.615	0.543			-0.004	-0.005	0.996			-0.076	-0.207	0.837
Age X Sex			0.540	0.601	0.553			0.313	0.210	0.840			0.202	0.356	0.724
Antipsychotics			-0.199	-1.102	0.280			-0.241	-0.765	0.469			-0.233	-1.625	0.112
BDNF			-0.178	-1.008	0.322			0.555	1.684	0.136			0.125	0.844	0.403

Dependent Variable: LNS	R^2 Change	Sig F. Change	Beta	t	Sig	R^2 Change	Sig F. Change	Beta	t	Sig	R^2 Change	Sig F. Change	Beta	t	Sig
BLOCK 1	0.287	0.067				0.408	0.498				0.263	0.037			
Self-reported race													0.114	0.731	0.469
Recruitment Site			-0.075	-0.375	0.710			2.050	1.701	0.133			-0.073	-0.335	0.740
Age			-0.435	-0.787	0.438			-1.005	-0.852	0.422			-0.236	-0.533	0.597
Sex			-0.415	-0.762	0.452			0.523	0.653	0.534			-0.021	-0.057	0.955

Age X Sex			-0.195	0.234	0.817			-1.541	-1.040	0.333			-0.238	-0.422	0.676
Antipsychotics			-0.138	-0.813	0.423			0.042	0.139	0.894			-0.162	-1.170	0.248
BLOCK 2	0.004	0.710				0.031	0.588				0.021	0.281			
Self-reported race													0.075	0.470	0.641
Recruitment Site			-0.071	-0.350	0.729			2.096	1.650	0.150			0.014	0.061	0.952
Age			-0.506	-0.854	0.400			-0.864	-0.683	0.520			-0.303	-0.680	0.500
Sex			-0.457	-0.810	0.425			0.655	0.750	0.482			-0.027	-0.074	0.941
Age X Sex			0.282	0.322	0.750			-1.672	-1.061	0.329			-0.191	-0.338	0.737
Antipsychotics			-0.125	-0.708	0.485			0.092	0.277	0.791			-0.138	-0.984	0.331
BDNF			0.064	0.375	0.710			0.197	0.573	0.588			0.159	1.092	0.281

Table 11. Additive and Interactive Effects on LM I in the Schizophrenia-Spectrum (N=50)

Dependent Variable: LM I	R^2 Change	Sig F. Change	Beta	t	Sig
BLOCK 1	0.260	0.035			
Self-reported race			0.172	1.106	0.275
Recruitment Site			-0.431	-1.952	0.057
Age			0.059	0.134	0.894
Sex			-0.006	-0.016	0.987
Age X Sex			-0.138	-0.251	0.803
Antipsychotics			-0.259	-1.887	0.066
BLOCK 2	0.005	0.861			
Self-reported race			0.151	0.920	0.363
Recruitment Site			-0.385	-1.582	0.121
Age			0.024	0.052	0.959
Sex			-0.005	-0.015	0.988
Age X Sex			-0.116	-0.203	0.840
Antipsychotics			-0.248	-1.720	0.093
COMT			0.006	0.039	0.969
BDNF			0.080	0.546	0.588
BLOCK 3	0.051	0.091			
Self-reported race			0.200	1.228	0.227
Recruitment Site			-0.454	-1.884	0.067
Age			0.081	0.181	0.858
Sex			0.041	0.115	0.909
Age X Sex			-0.177	-0.319	0.751
Antipsychotics			-0.245	-1.736	0.090
COMT			-0.260	-1.237	0.223
BDNF			-0.203	-0.934	0.356
COMT X BDNF Interaction			0.456	1.733	0.091

Table 12. Additive and Interactive Effects on LM II in the Schizophrenia-Spectrum (N=50)

Dependent Variable: LM II	R^2 Change	Sig F. Change	Beta	t	Sig
BLOCK 1	0.220	0.084			
Self-reported race			0.112	0.700	0.487
Recruitment Site			-0.402	-1.772	0.083
Age			-0.105	-0.234	0.816
Sex			-0.077	-0.212	0.833
Age X Sex			0.172	0.305	0.762
Antipsychotics			-0.251	-1.783	0.082
BLOCK 2	0.014	0.689			
Self-reported race			0.074	0.441	0.662
Recruitment Site			-0.342	-1.378	0.176
Age			-0.134	-0.287	0.776
Sex			-0.072	-0.194	0.847
Age X Sex			0.181	0.311	0.757
Antipsychotics			-0.226	-1.535	0.132
COMT			-0.036	-0.237	0.814
BDNF			0.127	0.844	0.404
BLOCK 3	0.012	0.652			
Self-reported race			0.098	0.572	0.570
Recruitment Site			-0.376	-1.486	0.145
Age			-0.106	-0.225	0.823
Sex			-0.049	-0.132	0.896
Age X Sex			0.151	0.258	0.798
Antipsychotics			-0.225	-1.517	0.137
COMT			-0.166	-0.750	0.458
BDNF			-0.012	-0.052	0.959
COMT X BDNF Interaction			0.223	0.807	0.424

Table 13. Additive and Interactive Effects on LNS in the Schizophrenia-Spectrum (N=60)

Dependent Variable: LNS	R^2 Change	Sig F. Change	Beta	t	Sig
BLOCK 1	0.263	0.037			
Self-reported race			0.114	0.731	0.469
Recruitment Site			-0.073	-0.335	0.740
Age			-0.236	-0.533	0.597
Sex			-0.021	-0.057	0.955
Age X Sex			-0.238	-0.422	0.676
Antipsychotics			-0.162	-1.170	0.248
BLOCK 2	0.077	0.109			
Self-reported race			0.032	0.204	0.839
Recruitment Site			-0.066	-0.286	0.775
Age			-0.125	-0.282	0.779
Sex			0.039	0.110	0.913
Age X Sex			-0.393	-0.703	0.486
Antipsychotics			-0.093	-0.676	0.503
COMT			-0.265	-1.850	0.072
BDNF			0.165	1.167	0.250
BLOCK 3	0.015	0.352			
Self-reported race			0.010	0.061	0.952
Recruitment Site			-0.026	-0.113	0.911
Age			-0.167	-0.373	0.711
Sex			0.003	0.008	0.994
Age X Sex			-0.344	-0.612	0.544
Antipsychotics			-0.095	-0.684	0.498
COMT			-0.119	-0.566	0.575
BDNF			0.319	1.474	0.148
COMT X BDNF Interaction			-0.245	-0.941	0.352

Table 14. GEE Analyses of COMT and BDNF in the Entire Sample (N=161)

	Dependent Variable: LM I		Dependent Variable: LM II		Dependent Variable: LNS	
	Wald χ^2	Sig.	Wald χ^2	Sig.	Wald χ^2	Sig.
Self-reported race	9.763	0.002	12.189	0.000	5.724	0.017
Age	5.897	0.015	0.093	0.760	10.514	0.001
Sex	1.960	0.162	8.695	0.003	0.939	0.333
Age X Sex	0.009	0.924	0.000	0.987	0.098	0.754
Antipsychotics	8.705	0.003	10.479	0.001	2.553	0.110
COMT	0.654	0.721	0.451	0.798	1.111	0.574
	QIC = 1372.292	QICC = 1371.269	QIC = 1307.240	QICC = 1307.207	QIC = 1277.427	QICC = 1276.104

(N = 146)

	Wald χ^2	Sig.	Wald χ^2	Sig.	Wald χ^2	Sig.
Self-reported race	10.643	0.001	11.143	0.001	5.716	0.017
Age	5.636	0.018	0.016	0.899	11.963	0.001
Sex	0.421	0.517	5.830	0.016	0.243	0.622
Age X Sex	0.085	0.771	0.016	0.898	0.430	0.512
Antipsychotics	7.710	0.005	6.209	0.013	4.030	0.045
BDNF	0.066	0.797	0.464	0.496	0.013	0.910
	QIC = 1252.612	QICC = 1251.892	QIC = 1203.107	QICC = 1203.059	QIC = 1153.232	QICC = 1152.867

	Wald χ^2	Sig.	Wald χ^2	Sig.	Wald χ^2	Sig.
Self-reported race	4.243	0.039	9.04	0.003	6.226	0.013
Age	4.613	0.032			13.809	0.000
Sex	6.916	0.009			0.273	0.601
Age X Sex	0.270	0.603			0.602	0.438
Antipsychotics	1.814	0.178			4.153	0.042
COMT	63.059	0.000	4.595	0.100	0.770	0.680
BDNF	14.949	0.000	1.121	0.290	0.000	1.000
COMT-BDNF Interaction	0.486	0.784	0.955	0.620	1.017	0.601
	QIC = 3069.891	QICC = 2991.291	QIC = 1314.494	QICC = 1311.191	QIC = 1146.718	QICC = 1146.392

*could not compute with all covariates included

Table 15. GEE Analyses of COMT and BDNF in the Entire Sample by Sex

	Dependent Variable: LM I		Dependent Variable: LM II		Dependent Variable: LNS	
Males (N = 83)	Wald χ^2	Sig.	Wald χ^2	Sig.	Wald χ^2	Sig.
Self-reported race	11.306	0.001	12.869	0.000	4.618	0.032
Age	1.589	0.207	0.24	0.624	3.775	0.052
Antipsychotics	1.526	0.217	1.815	0.178	0.027	0.869
COMT	0.845	0.655	1.746	0.418	0.900	0.637
BDNF	0.119	0.730	0.115	0.734	1.287	0.257
COMT-BDNF Interaction	13.914	0.001	18.642	0.000	15.566	0.000
	QIC = 684.758	QICC = 686.970	QIC = 630.261	QICC = 633.386	QIC = 511.835	QICC = 514.195

	Dependent Variable: LM I		Dependent Variable: LM II		Dependent Variable: LNS	
Females (N = 70)	Wald χ^2	Sig.	Wald χ^2	Sig.	Wald χ^2	Sig.
Self-reported race	2.688	0.101	4.334	0.037	1.698	0.193
Age	9.690	0.002	0.057	0.810	6.151	0.013
Antipsychotics	48.054	0.000	22.18	0.000	25.516	0.000
COMT	10.448	0.005	1.001	0.606	6.746	0.034
BDNF	2.958	0.085	4.887	0.027	3.475	0.062
COMT-BDNF Interaction	70.353	0.000	26.202	0.000	25.669	0.000
	QIC = 447.286	QICC = 456.040	QIC = 475.783	QICC = 483.079	QIC = 519.528	QICC = 527.668

Figure Captions:

1. COMT Gene and LD Plot from the HAPMAP project.

2. BDNF Gene and LD Plot from the HAPMAP project.

3. Logical Memory I (LM I) distribution

4. Logical Memory II (LM II) distribution

5. Letter-Number Sequencing (LNS) distribution

6. Diagnostic Group Differences in Logical Memory I Performance with self-reported race covariate

7. Diagnostic Group Differences in Logical Memory II Performance with self-reported race covariate

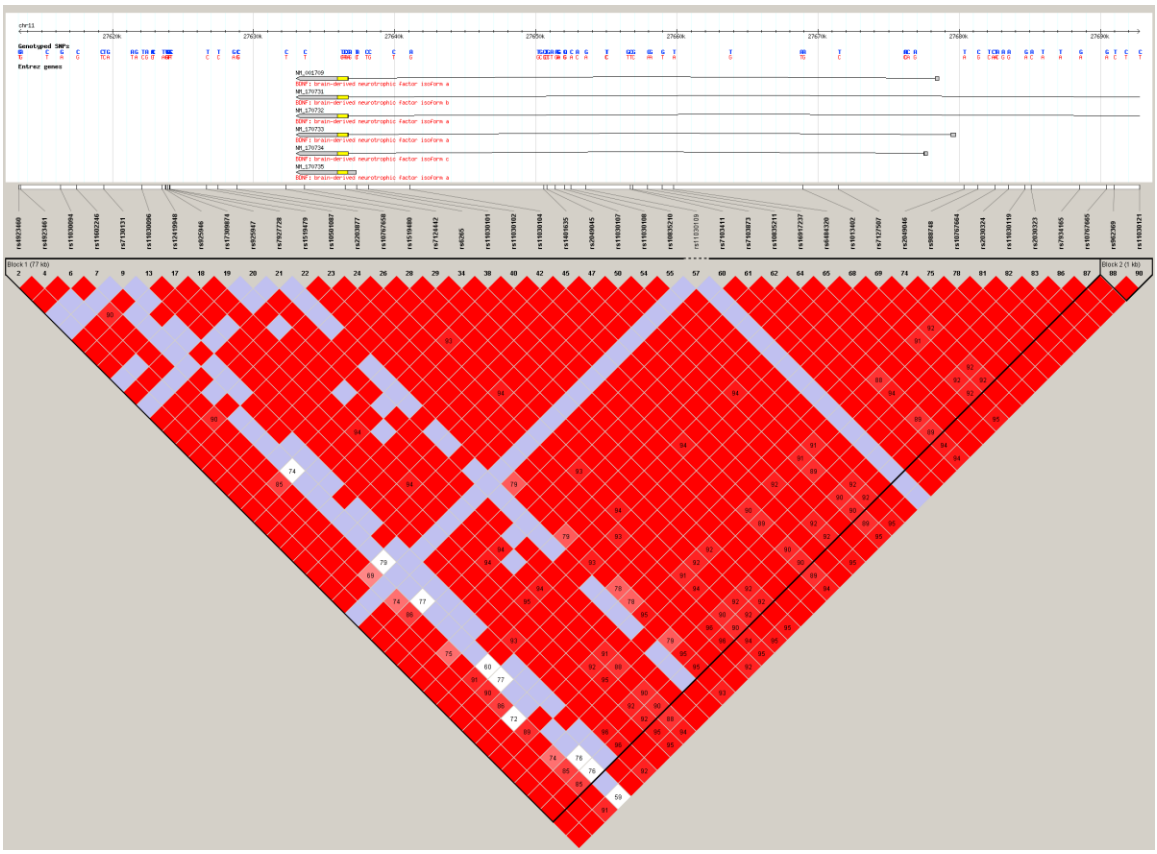
8. Diagnostic Group Differences in Letter-Number Sequencing Performance with self-reported race covaried.

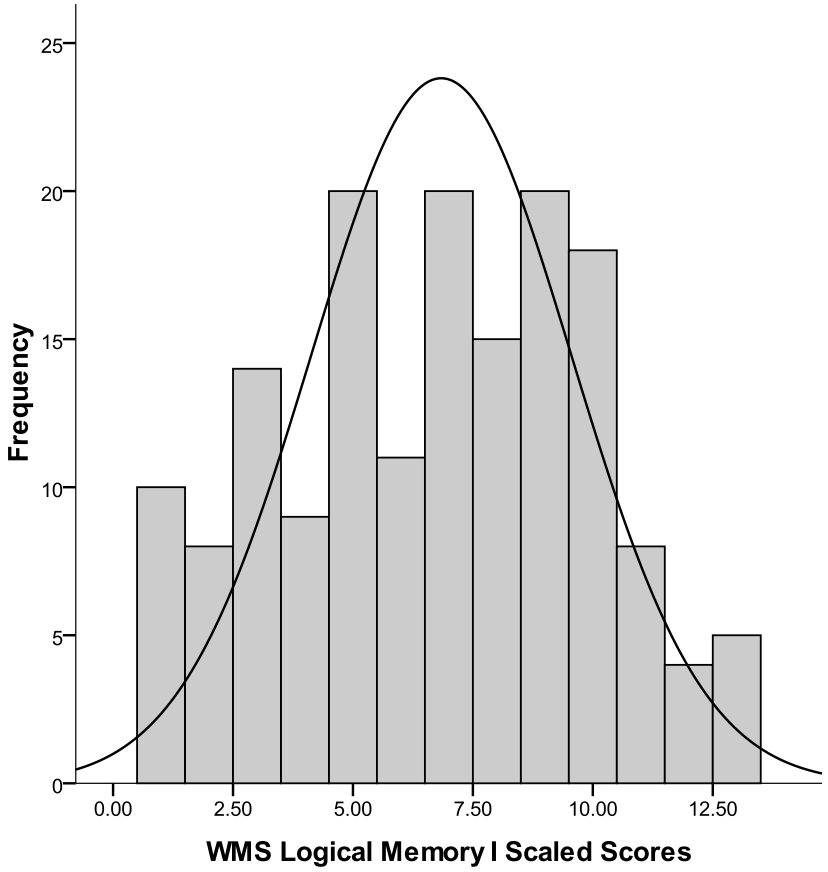
9. COMT predicts Letter-Number Sequencing Performance (Mean and SE) in CAU Sample with recruitment site, age, sex and the interaction between age and sex, and antipsychotic medication covaried.

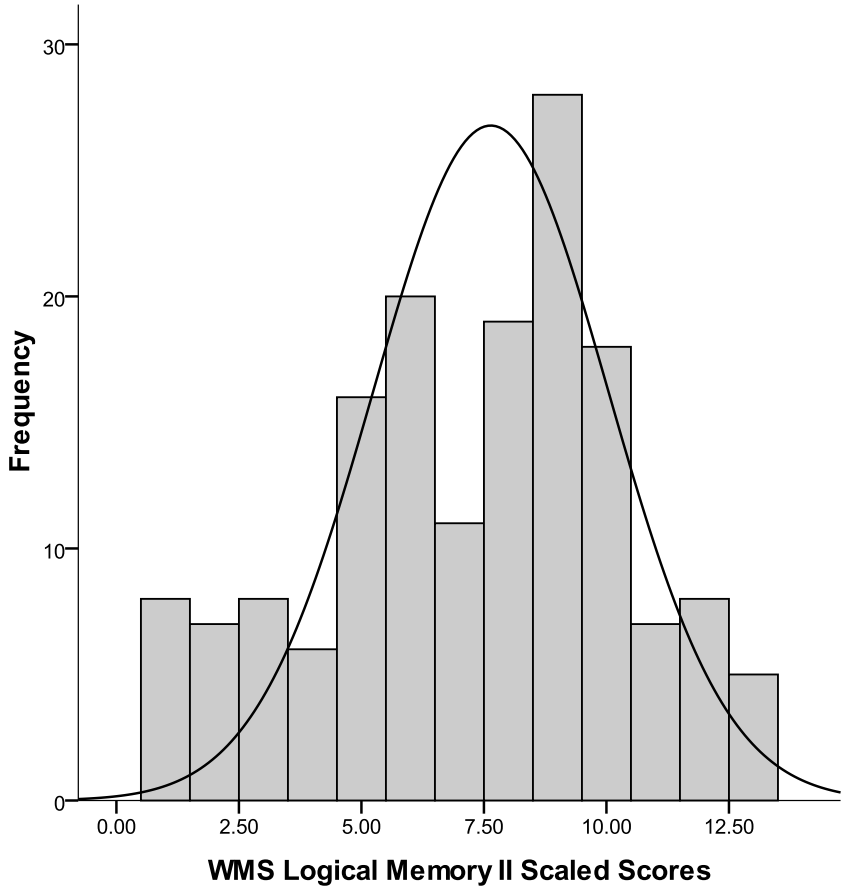
10. COMT predicts Letter-Number Sequencing Performance (Mean and SE) in Female Participants with self-reported race, age, sex and the interaction between age and sex, and antipsychotic medication covaried.

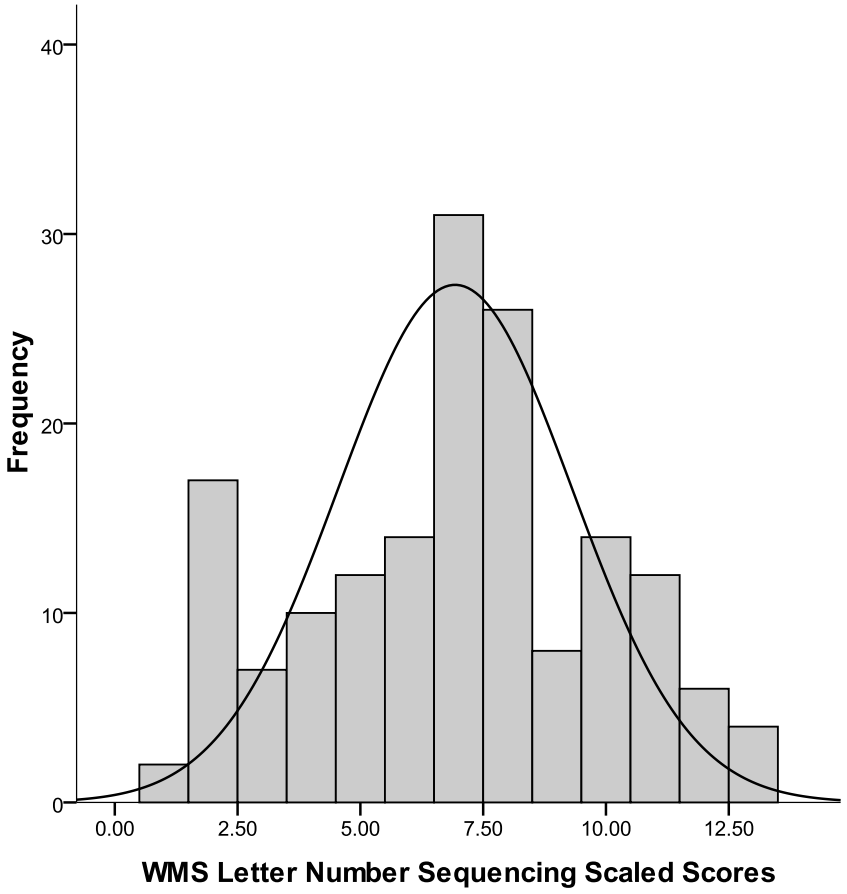
11. Interaction of COMT and BDNF predicts Verbal Memory Performance (Mean and SE) in Male Participants with self-reported race, age, and antipsychotic medication covaried.

12. Interaction of COMT and BDNF predicts Verbal Memory Performance (Mean and SE) in Female Participants with self-reported race, age, and antipsychotic medication covaried.


Genotyped SNPs
Entrez genes
BDNF brain-derived neurotrophic factor isoform a
BDNF brain-derived neurotrophic factor isoform b
BDNF brain-derived neurotrophic factor isoform c


Frequency
25
20
15
10
5
0
0.00
2.50
5.00
7.50
10.00
12.50
WMS Logical Memory I Scaled Scores


30
20
10
0
Frequency
0.00
2.50
5.00
7.50
10.00
12.50
WMS Logical Memory II Scaled Scores


Frequency
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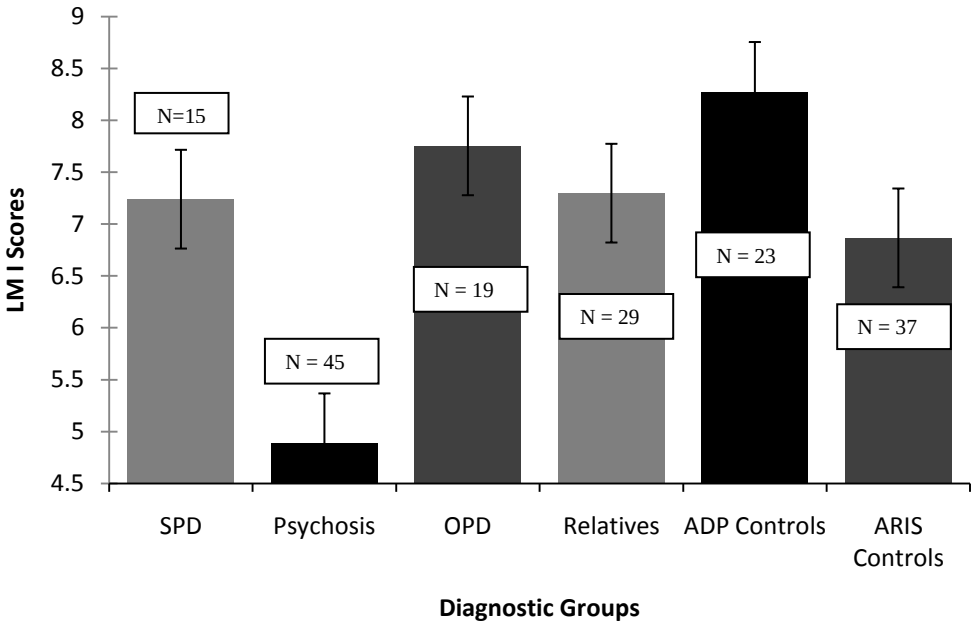
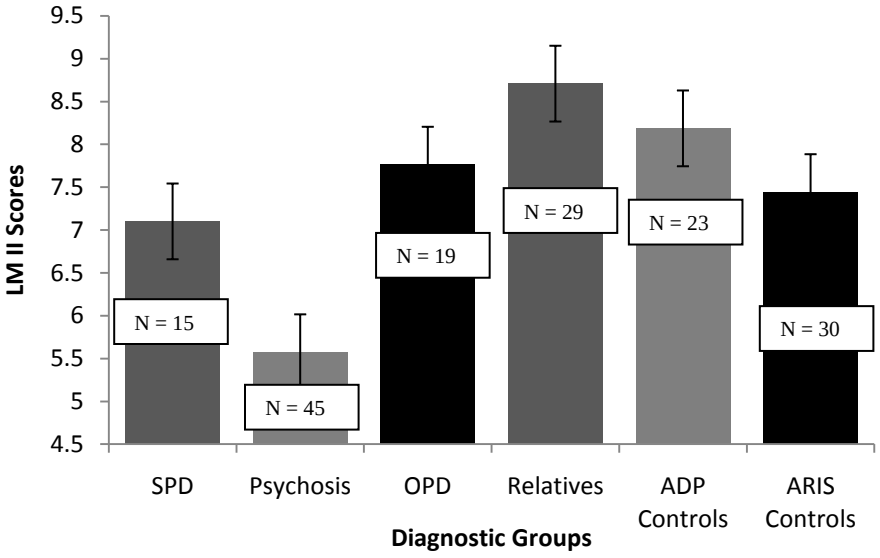
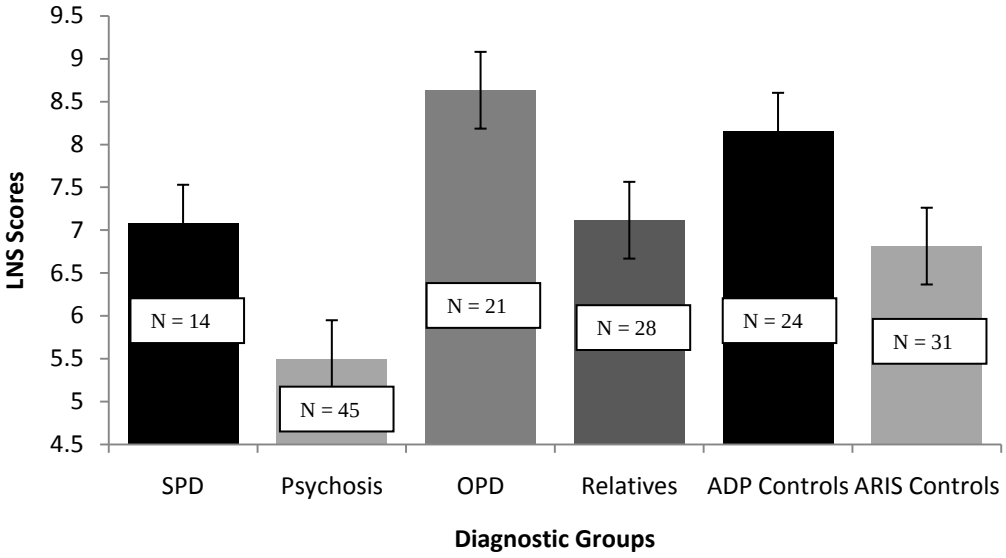
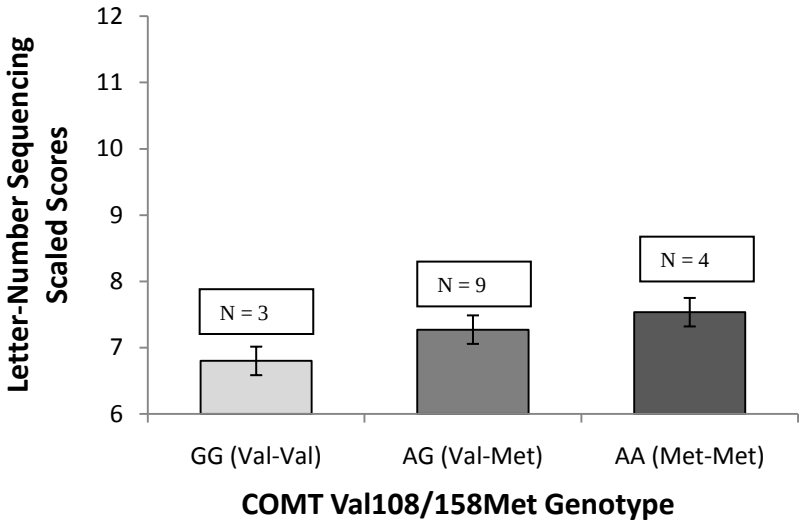
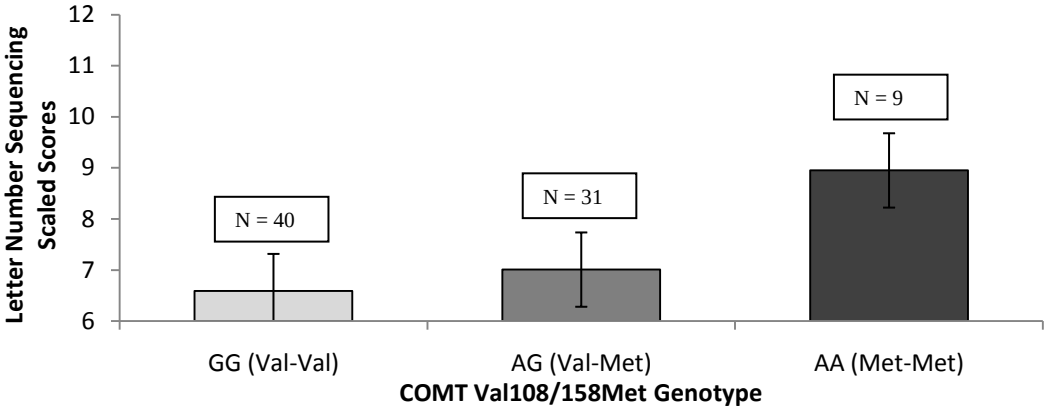
30
20
10
0
0.00
2.50
5.00
7.50
10.00
12.50
WMS Letter Number Sequencing Scaled Scores

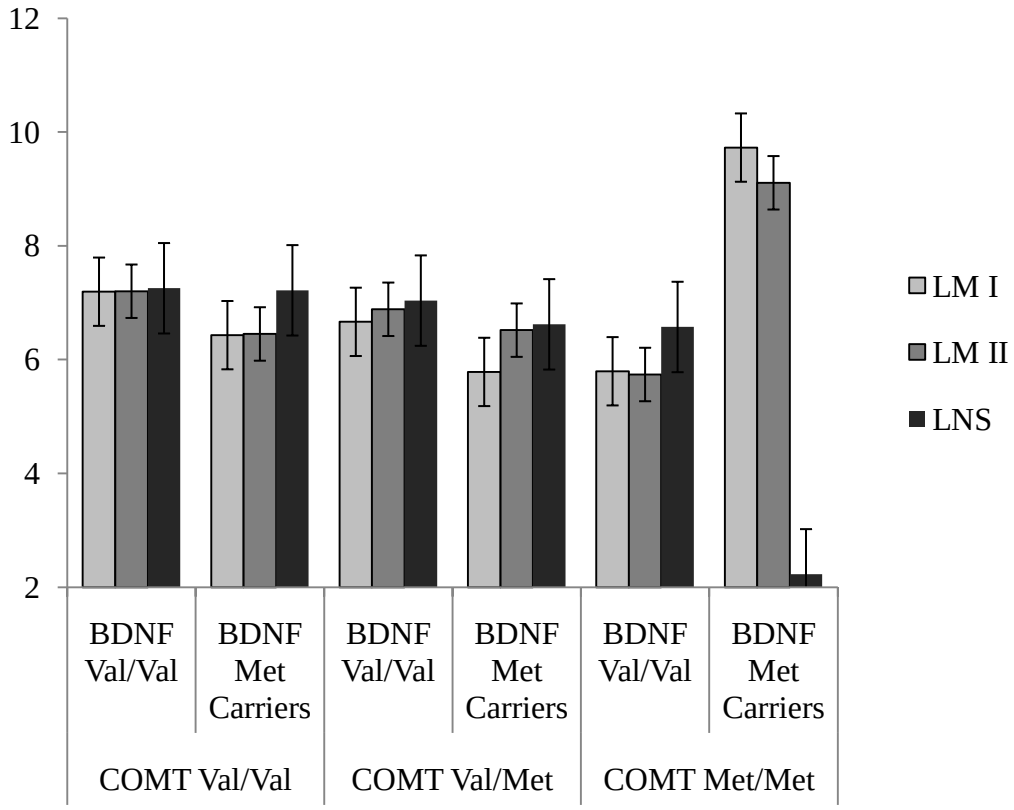

9
8.5
8
7.5
7
6.5
6
5.5
5
4.5
LM I Scores
N=15
N = 45
N = 19
N = 29
N = 23
N = 37
SPD
Psychosis
OPD
Relatives
ADP Controls
ARIS Controls
Diagnostic Groups

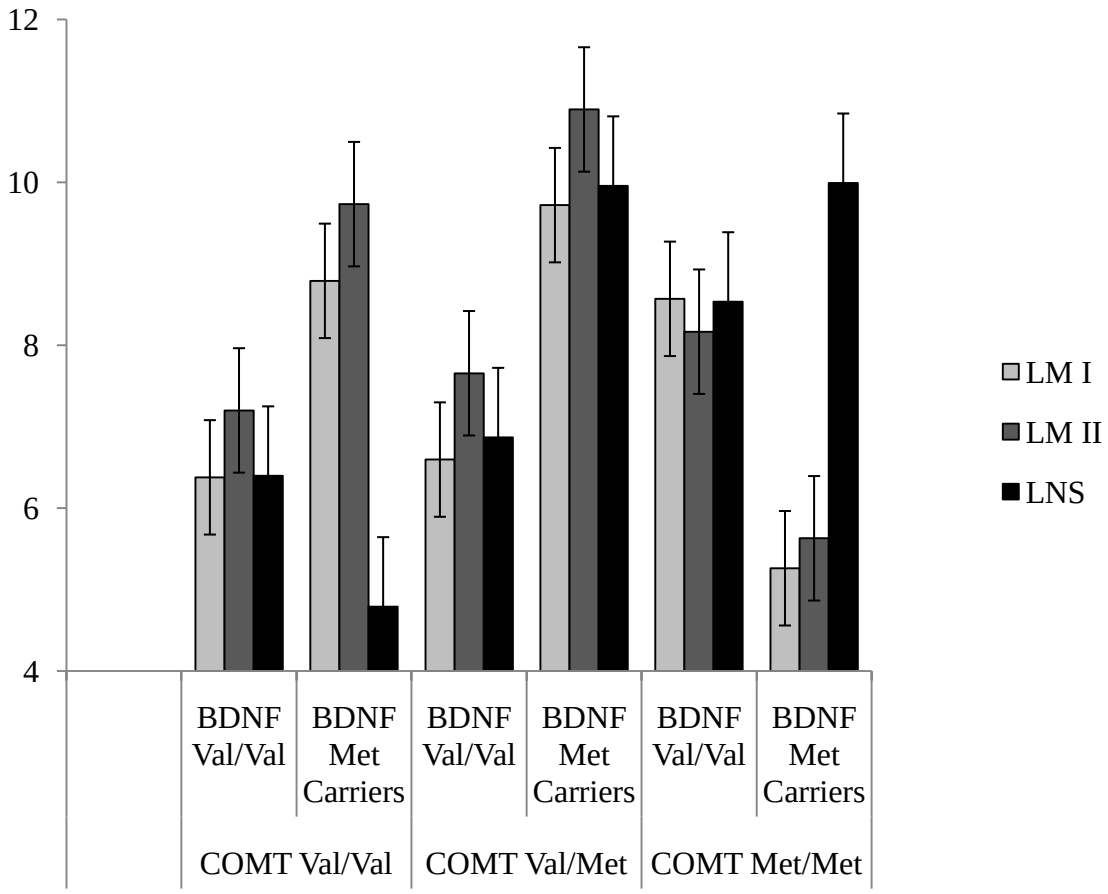

9.5
9
8.5
8
7.5
7
6.5
6
5.5
5
4.5
LM II Scores
N = 15
N = 45
N = 19
N = 29
N = 23
N = 30
SPD
Psychosis
OPD
Relatives
ADP Controls
ARIS Controls
Diagnostic Groups


9.5
9
8.5
8
7.5
7
6.5
6
5.5
5
4.5
LNS Scores
N = 14
N = 45
N = 21
N = 28
N = 24
N = 31
SPD
Psychosis
OPD
Relatives
ADP Controls
ARIS Controls
Diagnostic Groups


Letter-Number Sequencing
Scaled Scores
12
11
10
9
8
7
6
N = 3
N = 9
N = 4
GG (Val-Val)
AG (Val-Met)
AA (Met-Met)
COMT Val108/158Met Genotype


Letter Number Sequencing
Scaled Scores
12
11
10
9
8
7
6
N = 40
N = 31
N = 9
GG (Val-Val)
AG (Val-Met)
AA (Met-Met)
COMT Val108/158Met Genotype


12
10
8
6
4
2
LM I
LM II
LNS
BDNF Val/Val
BDNF Met Carriers
BDNF Val/Val
BDNF Met Carriers
BDNF Val/Val
BDNF Met Carriers
COMT Val/Val
COMT Val/Met
COMT Met/Met


12
10
8
6
4
LM I
LM II
LNS
BDNF Val/Val
BDNF Met Carriers
BDNF Val/Val
BDNF Met Carriers
BDNF Val/Val
BDNF Met Carriers
COMT Val/Val
COMT Val/Met
COMT Met/Met