Working Memory Subprocesses and Catechol-O-methyltransferase Val158Met Polymorphism in Schizophrenia Patients, Bipolar Disorder Patients, and Their Relatives

A DISSERTATION
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY

Daphne Dionisio

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

Scott R. Sponheim, Ph.D.
Matt McGue, Ph.D.

June 2010

ACKNOWLEDGEMENT

This research was derived from a study of the symptoms, cognition, and genetics of schizophrenia conducted through the Minneapolis Veterans Affairs Medical Center and Department of Psychology at the University of Minnesota. The CDG (Cognitive Deficits and Genetics) Study is supported by the Veterans Affairs Medical Research Program and the National Institutes of Mental Health with Scott R. Sponheim, Ph.D. as Principal Investigator. Scott Sponheim deserves special thanks for his guidance and patience on this project.

ABSTRACT

The present study had several objectives. It sought to determine if deficits in working memory subprocesses of maintenance, monitoring, and manipulation are specific to schizophrenia or are also present in patients with bipolar disorder. It was of interest to additionally determine if working memory deficits are present in the relatives of schizophrenia patients and relatives of bipolar disorder patients. Finally, the association between the *COMT* Val158Met polymorphism and working memory ability in schizophrenia patients, bipolar disorder patients, and the relatives of these patient groups was investigated.

Genotyping data and performance scores for the Spatial Delayed Response Task (i.e. maintenance), Self Ordered Pointing (i.e. monitoring), Digit Span Backwards (i.e. low demand manipulation) and Letter Number Sequencing (i.e. high demand manipulation) were collected for schizophrenia patients, bipolar disorder patients, relatives of schizophrenia patients, relatives of bipolar disorder patients, and nonpsychiatric controls. Results showed worse performance on the maintenance, low demand manipulation, and high demand manipulation working memory subprocesses for schizophrenia patients compared to nonpsychiatric controls and bipolar disorder patients. The relatives of schizophrenia patients also demonstrated impairment in low demand manipulation and high demand manipulation, as well as a trend for worse maintenance performance compared to nonpsychiatric controls. Although no genotype group differences were revealed when examined in a sample combining all diagnostic groups, a few genotype group differences were detected when examined within a sample of

schizophrenia patients. These results will be discussed. The results suggest that schizophrenia and bipolar disorder have distinct pathophysiologies, manipulation is promising as an endophenotype for schizophrenia-relevant disease genes, and there may be Val158Met genotype group differences in working memory within schizophrenia patients.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION AND LITERATURE REVIEW

Evolutionarily, the prefrontal cortex (PFC) is a recently developed structure considered to be responsible for the higher-order cognitive functions that are unique to humans and other higher primates. Informational and technological achievements of our species are a direct result of the human PFC's capacity for executive functions such as inhibition, abstraction, ordering, problem solving, and working memory. Not surprisingly, PFC abnormalities have been implicated in distinctively human afflictions such as psychiatric disorders. Within the research on mental illness, reports of patient PFC impairment are particularly widespread in schizophrenia.

Pathophysiology of Prefrontal Cortex in Schizophrenia

Neuroimaging research consistently demonstrates that schizophrenia patients have abnormal frontal lobe activation during tasks that require executive function (Andreasen et al., 1997; Barch, Sheline, Csernansky, & Snyder, 2003; Buchsbaum et al., 1992; Carter et al., 1998; Holmes, 2005; MacDonald III, & Carter, 2003; MacDonald III et al., 2005; Morey et al., 2005; Perlstein, Dixit, Carter, Noll, & Cohen, 2003; Walter et al., 2003; Weinberger & Berman, 1986). Furthermore, meta-analyses support the brain imaging findings of diminished activity in the prefrontal cortex of schizophrenia patients during cognitive tasks (Davidson & Heinrichs, 2003) as well as at rest (Hill et al., 2004).

It has been suggested that these prefrontal impairments are the result of physical pathology of the PFC. This view is supported by reports of compromised cellular organization of the dorsolateral PFC. Postmortem investigations have revealed reduced volume of neuronal bodies, diminished neuropil (i.e. unmyelinated axons and dendrites of

gray matter neurons), and compromised synapses in the dorsolateral PFC of schizophrenia patients (Lewis, 1997; Selemon & Goldman-Rakic, 1999; Selemon, Rajkowska, & Goldman-Rakic, 1995). Proton magnetic resonance spectroscopy, which can index the fitness of neuronal populations in living individuals by measuring concentrations of N-acetyl aspartate (NAA), has been measured in the frontal region of schizophrenia patients. Generally, NAA levels will positively correlate with health of neurons and processes. Studies have shown that schizophrenia patients have lower amounts of NAA in the frontal lobe in general (Pae et al., 2004), as well as in the dorsolateral PFC specifically (Bertolino et al., 1998a; Bertolino et al., 1998b; Bertolino & Weinberger 1999; Deicken, Zhou, Corwin, Vinogradov, & Weiner, 1997).

Working Memory Deficits in Schizophrenia

Generally, working memory has been described as a type of short-term memory within which internal representations of no-longer-available external stimuli, is held and processed to guide behavior for an impending task (Goldman-Rakic, 1994; D'Esposito, Postle, & Rypma, 2000; Stratta, Properini, Daneluzzo, Bustini, & Rossi, 2001). Electrophysiological research using primates has demonstrated that working memory is localized in the PFC (Goldman-Rakic, 1999b). Such research has shown that, during oculomotor as well as manual delayed response tasks of spatial working memory, neurons of the PFC increase their rate of firing during the delay stage where stimuli must be held online for an impending response (Goldman-Rakic, 1994, 1999b). Furthermore, it has been reported that when subjects produce errors during the delay period of such

tasks, single-unit recordings of corresponding PFC neurons indicate a commensurate failure of firing activity (Goldman-Rakic, 1999b).

Ever since it was presented as an alternative to the short-term memory paradigm of the late 1960's, Baddeley and Hitch's (1974) model of working memory has endured as the most widely accepted conceptualization of working memory. Baddeley's (2000) current version of the model consists of verbal, visuospatial, and episode (i.e. integrated verbal and visuospatial information) storage buffers as well as a central executive that coordinates the flow of information to, from, and between the three buffers. Although the central executive does coordinate basic maintenance of information in working memory, it also performs more complex functions of controlling and regulating processes regarding simultaneous tasks, switching between multiple strategies, selectively attending to relevant stimuli, inhibiting irrelevant stimuli, suppressing inappropriate behavior, switching of attention, and manipulation of retained material (Baddeley, 1996; Baddeley & Della Sala, 1998).

It has been proposed that working memory can be best understood if organized into distinct subprocesses (Baddeley, 1996; Baddeley & Hitch, 1974). Maintenance, monitoring, and manipulation have been researched as subprocesses of working memory. Maintenance would require only retaining information for impending use while monitoring might involve extensive updating of working memory contents. Manipulation would include not only maintenance but also the performance of cognitive operations upon the retained material (e.g sequencing or planning). In this view, the central executive not only coordinates the sensory storage buffers for the maintenance of

information in working memory, it is also capable of the higher-order functions of monitoring and manipulation.

Maintenance

One of the most consistent findings regarding working memory in schizophrenia is the observation that patients display impaired accuracy on spatial delayed response tasks. This type of task requires the participant to maintain in memory, the location of a briefly presented target cue and after a delay period, indicate the target's remembered-location. Delayed response tasks can be considered maintenance tasks of working memory. Schizophrenia patients are inaccurate regarding the target location when tested with the widely-used visuomotor version of the task (Carter, Mintun, Nichols, & Cohen, 1997; Chey, Lee, Kim, Kwon, Shin, 2002; Glahn, et al., 2006; Keefe et al., 1995; Kim, Glahn, Nuechterlein, & Cannon, 2004; Leiderman & Strejilevich, 2004; Minor & Park, 1999; Pukrop et al., 2003; Ross, Harris, Olincy, & Radant, 2000; Silver, Feldman, Bilker, & Gur, 2003; Snitz, Curtis, Zald, Katsanis, & Iacono, 1999; Spindler, Sullivan, Menon, Lim, & Pfefferbaum, 1997; Stratta, Properini, Daneluzzo, Bustini, & Rossi, 2001; Zuffante et al., 2001). This finding has also consistently held true for schizophrenia patients administered spatial delayed response tasks with an oculomotor approach (Everling, Krappman, Preuss, Brand, & Flohr, 1998; Krappmann, & Everling, 1998; McDowell et al., 2001; McDowell & Clementz, 1996; Park, 1997; Park, 1999; Park & Holzman, 1992; Park & Holzman, 1993; Park, Holzman, & Goldman-Rakic, 1995; Park, Puschel, Sauter, Rentsch, & Hell, 1999; Partiot et al., 1992; Raine et al., 1992; Ross et al.,

1998). This deficit has even been demonstrated in acutely psychotic (Park et al., 1999) as well as chronic (Silver et al., 2003) schizophrenia patients.

Only a single study has reported no differences between schizophrenia patients and healthy controls on a spatial delayed response task (Seidman et al., 1995). Examination of the methodology used in this study reveals that the researchers used an unorthodox approach to administering their version of a spatial delayed response task. Although it is conventional for the task to have several (usually eight) possible target locations, the Seidman group only required their participant to select from two target locations. Also, the task is usually conducted so that the participant is only briefly exposed to the target stimulus (e.g. a dot flashed in one of eight possible target locations). However, the spatial delayed response task of Seidman and colleagues involved opening a curtain that separated the experimenter and participant, the experimenter placing a penny in one of two wells, and then having the participant remember the target location while the curtain is closed during the delay period. Seidman et al. (1995) suggest that their inconsistent finding might be due to their task procedure, which they concede is considerably more simplistic than the conventional delayed response task approach.

Monitoring

Self-ordered working memory tasks generally involve presenting a participant with an array of items and for each trial, the participant must select only one item that s/he has never previously selected. For each trial, the locations of all the items in the array are randomly repositioned so that the participant can only rely upon her/his memory of the previously selected items rather than their location. It has been suggested that the

self-ordered tasks require working memory functions beyond mere maintenance as they additionally involve the monitoring (e.g. updating) of working memory contents (Conklin, Curtis, Calkins, & Iacono, 2005; Wagner & Smith, 2003).

A few investigations have examined self-ordered working memory tasks in schizophrenia. For all of these studies, schizophrenia patients exhibited less competence at the self-ordered task than normal controls (Chey et al., 2002; Conklin et al., 2005; Ganzevles & Haenen, 1995; Stone, Gabrieli, Stebbins, & Sullivan, 1998; Zuffante et al., 2001). Also, young individuals at very high risk for development of psychosis demonstrated a deficit in self-ordered task performance when compared to healthy adults (Wood et al., 2003). These researchers later found that, of the participants in the very high risk group, the ones who eventually developed psychosis had worse performance than those who did not.

Manipulation

While there is emerging interest in the parsing of working memory into various separable processes, substantial evidence is accumulating for a specific distinction between maintenance and manipulation. D'Esposito and colleagues have reported functional magnetic resonance imaging (fMRI) findings of greater dorsolateral PFC activation in healthy volunteers during manipulation than during maintenance conditions (D'Esposito et al., 1998; D'Esposito, Postle, Ballard, & Lease, 1999; Postle, Berger, D'Esposito, 1999). This greater dorsolateral PFC activation in healthy volunteers has been similarly observed during manipulation conditions even when compared to

conditions of increasing memory set size which places heavy demands upon maintenance (Glahn et al., 2002).

These working memory subprocesses have been compared in patients with schizophrenia. Kim, Glahn, Nuechterlien, & Cannon (2004) described that patients with this illness exhibited performance deficits when compared to controls during both maintenance-only as well as maintenance-and-manipulation conditions. They further reveal that, compared to controls, the patients' performance during the latter was disproportionately worse than in the former. Although it has been found that schizophrenia patients also produce greater dorsolateral PFC activation in manipulation versus maintenance conditions, their degree of increased activation is significantly less than that produced by healthy controls (Cannon et al., 2005; Tan, Choo, Fones, & Chee, 2005).

The Letter Number Sequencing task is a test from the Wechsler Adult Intelligence Scale, Third Edition-Revised (WAIS-III-R) that requires the participant to manipulate the contents of working memory. For each trial in this task, the participant is presented with increasingly longer strings of alternating letters and numbers and must first recite the numbers in ascending order followed by the letters in alphabetical order. Only a handful of published studies have compared schizophrenia patients to healthy adults on this test of working memory's manipulation subprocess. Each of these studies has found worse performance in the patients (Conklin et al., 2005; Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997; Goldberg et al., 1998; Pukrop et al., 2003). Consistent with the supposition that such sequencing taps higher order executive functions, McGurk et al.

(2004) indicated that Letter Number Sequencing ability correlated with scores from a well-known working memory test of set-shifting and inhibition (Wisconsin Card Sort Test, WCST) in their group of older, poor outcome schizophrenia patients.

In the Digit Span Backwards subtest of the WAIS-III-R, after being presented with a series of digits, the participant must recite the items in reverse order. Each trial consists of an increasingly longer series of digits. Performance on this test is considered to be a measure of working memory. Because the presented stimuli must be reversed, this task can more specifically address the working memory process of manipulation.

Regarding the Digit Span Backwards, only three studies found no working memory difference between schizophrenia patients and normal controls (Chan, Yip, & Lee, 2004; Chen, Chen, & Lieh-Mak, 2000; Park & Holzman, 1992). The majority of experiments that have compared these two groups on the Digit Span Backwards have reported impairment in schizophrenia patients (Alptekin et al., 2005; Bozikas, Kosmidis, Kiosseoglou, & Karavatos, 2006; Brebion, Amador, Smith, Gorman, 1998; Conklin et al., 2000; Conklin et al., 2005; Glahn et al., 2006; Karatekin & Asarnow, 1998; Kiefer, Apel, & Weisbrod, 2002; Moritz, et al. 2002; Muller et al. 2005; Salame, Danion, Peretti, & Cuervo, 1998; Silver et al., 2003; Stefansson & Jonsdottir, 1996; Stone et al., 1998; Stratta et al., 1997). A meta-analysis by Aleman, Hijman, de Haan, & Kahn (1999) also resulted in a large effect size for the Digit Span Backwards. Careful examination of the methodology of the three discrepant Digit Span Backwards studies yielded no irregularities that could account for the inconsistent results except perhaps their mutual lack of a control condition to verify intact maintenance ability.

To summarize, schizophrenia patients appear to have a deficit in the maintenance subprocess of working memory. The abundant findings of impaired patient performance on delayed response tasks support this assertion. Also, individuals with schizophrenia have been found to display faulty monitoring ability. Although only a few experiments have been conducted to examine this subprocess of working memory, every self-ordered pointing study has reported the deficit in the patients compared to healthy controls. Lastly, schizophrenia patients have consistently exhibited difficulty in the manipulation of temporarily stored information. This finding was a consistent result of many Digit Span Backwards investigations and has been reported for every Letter Number Sequencing study.

The Genetics of Schizophrenia

Multiple lines of epidemiological evidence converge in support of a substantial genetic component in schizophrenia. It has been reported that monozygotic twins are concordant for schizophrenia at a rate significantly greater than that of dizygotic twins: i.e. 48% vs. 17% (Gottesman, 1991). Despite the 1% prevalence in the general population, relatives of schizophrenia patients manifest greater disease risk with greater degree of relatedness (Gottesman, 1991). Although biological relatives of schizophrenic adoptees have higher rates of schizophrenia than control adoptees, children who are adopted by a parent who later develops schizophrenia do not go on to develop schizophrenia at an increased rate. Perhaps the most compelling epidemiological evidence comes from the finding that the offspring of monozygotic twins who are disconcordant for schizophrenia have equivalent rates of developing the condition

(Gottesman & Bertelson, 1989). Further support for a genetic component in schizophrenia comes from heritability estimates that are generally high: 65-85% (Cannon, Kaprio, Lonnqvist, Huttunen, & Koskenvuo, 1998) and 80% (Cardno & Gottesman, 2000; Sullivan, Kendler, & Neale, 2003).

Although genetic investigations have been able to identify the relevant gene(s) responsible for some illnesses with simple Mendelian inheritance where a single gene has major effect (e.g. Huntington's Disease), studies on illnesses with complex patterns of inheritance (e.g. most psychiatric disorders) have been less fruitful. Evidence that schizophrenia cannot be due to a single gene comes from examination of familial risk patterns (Risch, 1990). Epidemiological research largely supports a polygenic model in which there are multiple genes where each has small effect (Cannon, Gasperoni, van Erp, & Rosso, 2001). To this, the multifactorial model postulates an additional layer in which multiple environmental factors interact with polygenic loci to develop illness. Yet, according to McGue, Gottesman, & Rao (1985), data for twin concordance as well as degree of diminishing risk in first-, second-, and third-degree relatives does not reflect the additive gene effects that would be present in a multifactoral model. Instead, it is more likely that multiple epistatic gene-gene as well as gene-environment interactions are occurring in addition to additive gene effects. Because of this extremely complex additive and epistatic relationship, susceptibility genes will appear to account for a smaller share of genetic variance when examined individually (Kendler & Eaves, 2005).

To date, linkage studies in schizophrenia have yielded few consistent results (Weinberger, 2001). The lack of statistical power to detect genes of such small effect

may be the result of several potential impediments. False negatives may occur when susceptibility gene carriers are not classified as such. This may happen when clinical heterogeneity is created by conditions such as incomplete penetrance. For example, a carrier of predisposing genes might not reach diagnostic threshold if requisite environmental factors do not interact with such genes. False positives occur when patients, who appear to manifest the disease phenotype, do not actually share the same genotype. This causal heterogeneity can often be the result of phenocopies (i.e. when different causes appear to produce the same illness). For example, neurological damage from chronic substance abuse might manifest in schizophrenia-like symptoms. Also, according to Cannon et al. (2001), it is possible that locus heterogeneity arises when a variety of different gene combinations may lead to a similar schizophrenia phenotype.

The weak validity of current diagnostic criteria has been faulted as a chief reason for the array of false positives and negatives that plague the search for schizophrenia susceptibility genes. According to Risch & Merikangas (1996), the fallacious connection between genotype and clinical presentation undermines the ability to detect linkage even in studies that include thousands of affected sibling pairs. Gottesman and Bertelsen's (1989) finding of equal schizophrenia risk in the children of discordant monozygotic twins clearly indicates that clinical expression is not a true indicator of the presence of predisposing genes.

Working Memory Deficit as an Endophenotype in Relatives of Schizophrenia Patients

The diagnosis of schizophrenia is likely a manifestation of a complex array of defects of the central nervous system and probably reflects the sequelae of multiple

predisposing genes and environmental factors. To increase the statistical power of genetic studies, it has been proposed that the groups of interest need to be classified using an approach more objective than the traditional phenotype of clinical diagnosis (Cannon et al., 2000; Egan et al., 2001; Finkelstein, 1998; Ho, Wassink, O'Leary, Sheffield, & Andreasen, 2005; Sponheim, Iacono, Thuras, & Beiser, 2001). Intermediate phenotypes are more reliably present and measurable in individuals who possess the relevant genotype. Theoretically, these endophenotypes are the direct product or effect of a particular genotype and can be used as a behavioral or biological indicator of the presence of disease-relevant genes. Its use provides a more direct means of studying the expression of illness genotypes (Cannon, 2005). The unaffected relatives of schizophrenia patients are carriers of genes that predispose for the illness. The power of molecular genetic studies can be increased by the inclusion of relatives who carry the disease gene(s), as reflected by the presence of an endophenotype of schizophrenia, despite the fact that the relatives may not express the clinically recognized disorder (Cannon et al., 2001; Cannon et al., 2000).

Callicott et al. (2003) reported that schizophrenia patients and their non-schizophrenic siblings demonstrated similarly excessive fMRI response in the right dorsolateral PFC during a working memory task. This finding suggests that genetic vulnerability for the disease is expressed more strongly by way of cognition than by way of clinical diagnosis. According to Weinberger (2005), although the various schizophrenia-relevant genes each have small effect on clinical expression, they exact much greater effect at the level of cortical function. The relatives of schizophrenia

patients are ideal candidates for experimental investigation because they carry the genetic liability for the disease but are free of the confounding variables inherent in patient populations (e.g. lower education levels, chronic hospitalization, medication effects).

A considerable number of investigators have proposed working memory function as a promising candidate endophenotype for schizophrenia as much evidence indicates it is related to genetic risk for the disorder. Goldberg et al. (1995) reported that among monozygotic twins discordant for schizophrenia, the unaffected twins exhibited WCST performance intermediate between the affected twins and healthy twin controls. The difference between unaffected and control twins trended toward significance. Cannon et al. (2000) compared monozygotic and dizygotic twins discordant for schizophrenia and found greater degree of spatial working memory deficits with increasing degree of shared genes. In a similar vein, Glahn and colleagues examined spatial working memory function in healthy control twins as well as monozygotic and dizygotic twins discordant for schizophrenia. They found that greater working memory impairment was associated with greater genetic loading of disease genes (Glahn et al., 2003).

Maintenance

A small number of experiments have been conducted on the relatives of schizophrenia patients using the Spatial Delayed Response Task. Of these few experiments examining the maintenance subprocess of working memory, two have found that the relatives of patients demonstrated less accuracy than controls on the oculomotor version (McDowell et al., 2001; Park, Holzman, & Goldman-Rakic, 1995). Meanwhile, another oculomotor experiment reported the unusual finding of less accuracy among

parents of schizophrenia patients who had a negative family history of the disease although this was not found to be true for the parents with a positive history of the disorder (Ross et al., 1998). It should be noted that the these researchers classified the parents as positive- or negative-family history based upon interviews with the parents themselves as well as from reports by other relatives identifying a "potential schizophrenic relative." Therefore, in this study, the validity of the family history classification may be questionable. In a recent meta-analysis that included examination of Spatial Delayed Response Task accuracy, the effect size for the difference between patients' relatives and controls was among the largest effect sizes revealed (Snitz, MacDonald III, & Carter, 2006).

Schizotypal offspring of schizophrenia patients have been found to have age-related deficits on the oculomotor version of the Spatial Delayed Response Task when compared to controls and nonschizoptypal offspring of patients (Diwadkar, Montrose, Dworakowski, Sweeney, & Keshavan, 2006). The authors interpret this finding as evidence that schizotypal offspring experience increasing working memory impairment as they reach the common age of onset for schizophrenia. Clinically high risk adolescents (i.e. exhibiting prodromal symptoms of schizophrenia) have been investigated as well and were shown to be less accurate on the task than low risk controls (Smith, Park, & Cornblatt, 2006). Furthermore, it was observed that high risk offspring of patients produced less fMRI activation in the dorsolateral PFC and inferior parietal cortex while performing this task (Keshavan et al., 2002). Although the degree of genetic vulnerability in the prodromal high risk adolescents cannot be ascertained from the

information provided in the Smith et al. (2006) article, the findings regarding schizotypal and high risk offspring of schizophrenia patients provide support for the suggestion that genetic risk for schizophrenia is associated with impacted performance on the Spatial Delayed Response Task.

Monitoring

With regard to the monitoring subprocess of working memory, only two experiments were found that evaluated the ability of patients' relatives on self-ordered tasks. Conklin et al. (2005) reported that healthy controls required fewer trials than the relatives to solve the task. Unfortunately, the only other study converted the self-ordered task performance scores to z-scores to average them with scores from various other tasks (Staal, Hijman, Hulshoff Pol, & Kahn, 2000). For example, the investigators pooled and averaged z-scores from the Digit Span Forwards and two self-ordered tests to analyze the results of these tasks together under an Attention task domain. While differences were found in the Attention domain between patients and controls as well as patients and relatives, there was no significant difference between relatives and controls. Because the z-scores for various tasks were pooled, it is not possible to report on group differences on the self-ordered tasks per se. Also, an experiment that assessed youth at ultra high risk for psychosis found that this group made more errors on a self-ordered search task than the normal comparison group (Wood et al., 2003).

Manipulation

Working memory tasks like the Letter Number Sequencing and Digit Span Backwards tasks, which tap the manipulation subprocess have also been investigated in

the relatives of patients. Only one study measured Letter Number Sequencing in the relatives; this study found that relatives performed this task better than the patients but worse than the healthy controls (Conklin et al., 2005). Four studies in the existing literature have reported that the patients' relatives exhibit a deficit on the Digit Span Backwards version compared to controls (Conklin et al., 2000; Conklin et al., 2005; Laurent et al., 1999; Trandafir, Meary, Schurhoff, Leboyer, & Szoke, 2006). Uleland, Oie, Landro, & Rund. (2004) indicated that their group of adolescents with schizophrenia spectrum disorders also showed this deficit. Regarding the Digit Span Backwards, the Snitz et al. (2006) meta analysis reported a small to medium effect size for the performance difference between patients' relatives and normal controls.

However, seven other studies failed to find any difference between relatives and healthy volunteers on the Digit Span Backwards (Appels et al., 2003; Chen et al., 2000; Gochman et al., 2004; Ismail, Cantor-Graae, & McNiel, 2000; Keri, Kelemen, Benedek & Janka, 2001; Schubert, & McNeil, 2005; Shedlack et al., 1997). There are several possible explanations for why no difference was revealed. Relatives who consent to participate could be fundamentally different than relatives who could not be contacted or chose not to participate. That is, recruitment of patients' relatives may have been susceptible to a bias toward higher functioning parents and siblings who likely have less genetic risk for the disorder. In fact, Ismail and colleagues (Ismail et al., 2000) conceded that the attrition rate among their group of patients' siblings was high. Perhaps if the ultimately noncompliant relatives instead continued to participate, the results regarding group differences would have been very different. Also, Keri et al. (2001) pointed out

that their group of patients had a milder course of illness and that their relatives had high IQ, education, and psychosocial functioning. It is possible that this group of relatives is not representative of a genetically at-risk population. Of these studies that did not find Digit Span Backwards differences between the patients' relatives and the healthy controls, most of the investigators pointed out that their sample sizes were small. So it is possible that many of these studies lacked the statistical power necessary to reveal any group differences.

In summary, several lines of evidence indicate that a genetic component for working memory is conferred more often than the psychiatric condition. This would suggest that working memory function would be a better index of genetic diathesis than clinical diagnosis. Investigations that focus on the relatives of schizophrenia patients can provide an attractive means of examining the usefulness of working memory deficits as an endophenotype for genetic liability to schizophrenia. The few studies that have assessed the maintenance subprocess of working memory performance on the Spatial Delayed Response Task have generally shown impairment in the relatives of schizophrenia patients. Regarding the monitoring subprocess of working memory, the conflicting findings of only two self-ordered test studies have been reported for relatives. Clearly, there is a need to further investigate the monitoring subprocess to more fully examine high levels of manipulation during working memory subprocesses. For experiments on the manipulation component of working memory in schizophrenia patients' relatives, the only study that examined the Letter-Number Sequencing task revealed impairment in the relatives. The manipulation function of the Digit Span

Backwards has also been examined but the findings have not been consistent. In a review of meta-analyses assessing the relatives of schizophrenia patients, Heydebrand (2006) stated that a deficit on so-called "maintenance-plus" executive tasks (i.e. monitoring, manipulation, etc.) was the most consistent impairment revealed.

Specificity of the Working Memory Deficit Among Bipolar Disorder Patients

It is important to determine whether the widely reported observations of neuropsychological deficits in schizophrenia patients are specific to that illness or common to psychiatric disorders in general. As currently prevailing theories regarding the pathophysiology of schizophrenia have implicated the dorsolateral PFC, there is much interest in specifically determining if executive cognition, such as working memory function, is affected in bipolar disorder. Among psychiatric illness groups, bipolar disorder patients constitute a particularly desirable comparison group for schizophrenia patients as both illnesses are commonly associated with premorbid impairment, psychosis, clinically disorganized presentation, and mood-related symptoms. Working memory impairment in bipolar disorder patients might suggest that such deficits are associated with symptom severity and are general to psychiatric illness rather than specific to schizophrenia. Unfortunately, very few studies have been conducted to specifically investigate working memory performance in bipolar disorder and even less have compared this executive ability between this bipolar disorder and schizophrenia. Furthermore, the extant literature addressing this matter has been inconsistent.

Review of Evidence Reporting Intact Working Memory in Bipolar Disorder

There have been reports from several studies to suggest that affective disorders do not confer a deficit in working memory. Park (1997) and Park and Holzman (1992; 1993) reported that their groups of schizophrenia patients evinced dysfunction on an oculomotor delayed response working memory task while their group of bipolar disorder patients did not. Similarly, Clark, Iversen, and Goodwin (2001) did not find significant performance differences between their groups of healthy controls and bipolar disorder patients with mania on the Cambridge Neuropsychological Test Automated Battery (CANTAB) spatial working memory test. According to Harmer, Clark, Grayson, and Goodwin, (2002), working memory impairment is not a core component of bipolar disorder.

Review of Evidence Reporting a Working Memory Deficit in Bipolar Disorder

According to Coffman, Borenstein, Olson, Schwartzkopf, and Nasrallah (1990), neuropsychological deficits have been routinely reported in bipolar disorder patients. The findings of some studies have pointed to the performance difficulties of bipolar disorder patients on tests that include aspects of working memory (Coffman et al., 1990; Ferrier, Stanton, Kelly, & Scott, 1999). On a spatial working memory task (i.e. self-ordered searching) of the CANTAB, Sweeney, Kmiec, and Kupfer (2000) described their group of mixed and manic bipolar disorder patients as having a performance detriment when compared to healthy controls. In several investigations that had compared bipolar disorder patients and healthy controls, the patient group demonstrated impaired working memory on the Digit Span Backwards while their performance on the Digit Span

Forward remained intact (Ferrier et al., 1999; Gourovitch et al., 1999; Thompson et al., 2005).

Furthermore, despite the belief that cognitive impairment recedes with episode recovery, various reports indicate that neuropsychological deficits endure into the euthymic and remission phases of the bipolar disorder (Asarnow & MacCrimmon, 1981; Bearden, Hoffman, & Cannon, 2001; Coffman et al., 1990; Ferrier & Thompson, 2002; Ferrier et al., 1999; Hawkins et al., 1997; Kusumo & Vaughn, 1997; Seidman, 2002; Tam, Sewell, & Deng, 1998; Zubieta, Huguelet, O'Neil, Giordani, 2001). Such deficits have been shown to include executive function (Cavanagh, Beck, Muir, and Blackwood, 2002; Van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998; Zubieta et al., 2001). Studies have submitted evidence to suggest that deficits in working memory are among the cognitive impairments that persist into periods of euthymia. When compared to nonpsychiatric controls, individuals with euthymic bipolar disorder have exhibited working memory deficits on self-ordered pointing and Digits Span Backwards tasks but no difference on Digits Span Forwards (Thompson et al., 2000; Thompson et al., 2001a; Thompson et al., 2001b; Thompson et al., 2005).

Additionally, euthymic bipolar disorder patients have displayed less competence, but more brain activation, during an n-back working memory task (a spatial and object working memory n-back version) when compared to healthy controls (Adler, Holland, Schmithorst, Tchfarber, & Strakowski, 2004). The brain activation of the healthy controls and the bipolar disorder patients were in the dorsolateral PFC as well as other areas that have previously been identified as part of the working memory circuitry. The

authors proposed that the increased blood flow of the patient group in these areas likely reflects a difference in cognitive or physiological strategy. Support for this notion comes from the results of various brain imaging investigations that suggest functional or structural irregularity within euthymic bipolar disorder patients (Courtney, Ungerleider, Keil, Haxby, 1997; Goldman-Rakic 1996; Strakowski, Delbello, Adler, Cecil, & Sax, 2000). These findings are in contrast to another fMRI investigation that compared the n-back skills of healthy controls and euthymic bipolar disorder patients (Monks et al., 2004). Although there were no performance differences, the bipolar disorder patients produced less activation in frontal, temporal, and parietal areas. The authors concluded that the patients are less able to utilize frontal lobe networks relevant to executive cognition.

Review of Evidence Comparing Working Memory Performance Between Bipolar Disorder Patients and Schizophrenia Patients

In his review regarding cognitive differences between schizophrenia and bipolar disorder, Goldberg (1999) stated that the greater working memory impairment of the former population uniquely distinguishes it from bipolar disorder. There are some researchers who concede that bipolar disorder patients do indeed exhibit working memory deficits however, these researchers insist such impairment is much worse in schizophrenia patients. Gourovitch et al. (1999) compared monozygotic twins discordant for bipolar disorder to healthy, monozygotic twin controls on a battery of tests to include the Brown-Petersen memory task (i.e. verbal working memory task with distraction delay). The procedure for the Brown-Petersen task involves participants being presented

with four words that must be recalled after a 15-sec distraction delay requiring the naming of colors. Although there were no differences on the Digit Span Forwards or Backwards, on the Brown-Petersen task, the healthy control group scored a greater number of total correct responses than the unaffected twin group, which scored better than the affected twin group. Also, the healthy group created less task intrusions than the affected twin group, which produced fewer intrusions than the unaffected twin group. According to the researchers, this surprising latter finding may be because the affected twins understand their propensity for errors and consequently performed more cautiously while the unaffected twin group may not yet recognize their own deficits and thus responded with less inhibition. Despite these findings, Gourovitch and colleagues argue that the cognitive insufficiency of these bipolar disorder groups was much less severe than an earlier-studied group of schizophrenia patients (Goldberg et al., 1990).

Gooding and Tallent (2001) compared schizophrenia and bipolar disorder patients on tests of spatial working memory (i.e. Spatial Delayed Response Task) and inhibition (i.e. antisaccade task). The authors hypothesized that both patient groups would show difficulty in inhibition. Of particular interest then, was whether the inhibition impairment in both groups is mediated by working memory ability. On the Spatial Delayed Response Task, the schizophrenia group was less accurate than the bipolar disorder and nonpsychiatric control groups. Although the bipolar disorder group was somewhat less accurate than the control group, this difference was not significant. Also on this task, the schizophrenia group was slower than the bipolar disorder group, which was slower than the control group. The results for the antisaccade task were similar: schizophrenia

patients produced more errors than the bipolar disorder patients, who made more errors than the controls. The authors found a correlation between antisaccade and Spatial Delayed Response Task performance only in the schizophrenia group and, using mediational analysis, they further demonstrated that the antisaccade task performance in this patient group was mediated by working memory ability. Therefore, the authors concluded that although both patient groups exhibited inhibition impairment, the underlying mechanism for the impairment is different in these two groups. According to Gooding and Tallent, poor antisaccade performance in the bipolar disorder patients is likely due to impulsivity-related disinhibition, while in schizophrenia, the disinhibition is associated with working memory. These findings lend support to the view that similar cognitive defects in schizophrenia and bipolar disorder are the result of different pathophysiological processes.

In contrast to the aforementioned body of research, one study by Glahn et al. (2006) reported equally poor Digit Span Backwards performance among bipolar disorder (with as well as without psychosis), schizoaffective, and schizophrenia patients compared to nonpsychiatric controls. The results further indicated that, regardless of illness group, patients with a lifetime history of psychosis demonstrated compromised ability on their version of the Spatial Delayed Response Task. Also, examination of their version of the Spatial Delayed Response Task reveals a procedure very different from that conventionally used to assess the maintenance subprocess of working memory. Traditional Spatial Delayed Response Tasks have typically measured accuracy in terms of distance, in millimeters, between the actual location of a briefly flashing single target

stimulus and the participant's response estimating that location. However, in the Glahn study, participants were presented up to five simultaneous target stimuli for two seconds and performance was recorded as trials that were either correct or incorrect. It is possible that this task approach differs from conventionally-used procedures to a degree that might interfere with the results being directly comparable to the findings of the existing body of research.

Summary of Working Memory in Bipolar Disorder

With regard to the maintenance subprocess of working memory as measured by Spatial Delayed Response Task, studies have generally revealed no differences between bipolar disorder patient and control groups. With the exception of Glahn et al. (2006), who used an unconventional task procedure, every study that has included schizophrenia patients has reported a worse deficit in the schizophrenia patients compared to the bipolar disorder patients. Regarding the monitoring subprocess of working memory as measured by self-ordered or n-back tasks, studies have revealed worse performance in bipolar disorder patients compared to nonpsychiatric controls. However, the only study that included schizophrenia patients in the assessment found that they were impaired on monitoring while the bipolar disorder group was not (Badcock, Michie, & Rock, 2005). On the Digit Span Backwards test, which reflects the working memory subprocess of manipulation, studies have found impairment in bipolar disorder patients relative to controls (Ferrier et al., 2000; Thompson et al., 2000). Glahn et al. (2006) has been the only study to directly compare bipolar disorder and schizophrenia patient groups on the Digit Span Backwards. Although Glahn and colleagues reported impairment in these

patient groups compared to healthy controls, their calculation of the score did not incorporate the Forwards condition as a baseline control. The only other study to examine schizophrenia patients reported that although their bipolar disorder patients were impaired, the impairment was not as severe as that in an earlier studied group of schizophrenia patients (Gourovitch et al., 1999).

In sum, it appears very consistent that schizophrenia patients have a deficit in all three subprocesses of working memory. For bipolar disorder patients however, the evidence most strongly supports the perspective that although bipolar disorder patients may have some working memory deficits, they are likely not as severe as those in schizophrenia patients. It is critical to note that very few studies have been done to directly compare schizophrenia and bipolar disorder on these subprocesses. However, of the few studies that have compared schizophrenia and bipolar disorder patients, all but one has revealed a more severe deficit in schizophrenia. According to Bearden et al. (2001), the performance of bipolar disorder patients on neurocognitive tests is generally worse than that of nonpsychiatric controls but better than that of schizophrenia patients. Consequently, it has been suggested that the differential degree of impairment in these illnesses reflects differential pathophysiology. However, it is also possible that cognitive impairments demonstrated by bipolar disorder patients might be a consequence of factors such as general psychiatric state, disease-specific brain pathology, or a genotype specific to bipolar disorder.

Working Memory Performance in Relatives of Bipolar Disorder Patients

The scant data regarding working memory performance in relatives of bipolar disorder patients have been mixed and not easily comparable due to inclusion of different participant groups. Ferrier, Chowdhury, Thompson, Watson, and Young (2004) found that unaffected first-degree relatives of individuals with bipolar disorder showed greater impairment than nonpsychiatric controls on verbal (i.e. Digit Span Backwards) and visual (i.e. CANTAB spatial span) tests of working memory. A couple of studies have compared twins discordant for bipolar disorder and reported that the ill twin group performed worse than the non-ill co-twin group on the Digit Span Backwards, Visual Span Backward, and the Brown-Petersen task (Gourovitch et al., 1999; Kieseppa et al., 2004). This finding seems to suggest that working memory impairment in bipolar disorder is associated with clinical state rather than genetic liability. Only one study exists that compared relatives of schizophrenia and bipolar disorder patients. Keri et al. (2001), reported that the siblings of individuals with schizophrenia, but not healthy controls or the siblings of individuals with bipolar disorder, evidenced inadequate ability on a spatial working memory task. No differences were reported between the groups on forward or backward versions of the Digit Span. In summary, these few findings generally seem to parallel the studies have compared bipolar disorder and schizophrenia patients: the relatives of bipolar disorder patients may have some working memory impairments but probably not to the degree of severity found in the relatives of schizophrenia patients. Although the overall pattern of evidence seems to suggest that working memory impairment may not be an endophenotype for bipolar disorder, this

does not preclude the possibility that other endophenotypes exist for this likely genetically-influenced condition.

COMT

The finding that schizophrenia patients and their clinically healthy relatives both exhibit impaired executive function indicates that alleles that uniquely impact prefrontal cognition may predispose schizophrenia. Among the proposed candidate genes for schizophrenia, is *COMT* whose protein product is an enzyme called catechol-O-methyltransferase (COMT). This enzyme metabolizes catecholamines such as dopamine. *COMT* is uniquely interesting for several reasons. Unlike many of the other candidate genes, *COMT*'s polymorphisms are functional and their effects on dopamine catabolism demonstrate a clear mechanism by which neurocognition in schizophrenia can be influenced. The *COMT* gene is located at chromosomal area 22q11. Velocardiofacial syndrome (VCFS) is the result of a deletion in this area and it has been found that VCFS patients have increased risk for schizophrenia (Harrison & Weinberger, 2004). Also, the occurrence of 22q11 deletion happens significantly more often in schizophrenia patients than in the general population (Karayiorgou et al., 1995). Furthermore, several linkage studies suggest that this region of the genome is associated with schizophrenia (Lewis et al., 2003).

If *COMT*'s sequence of bases contains guanine at position 472 in long mRNA (position 322 in short mRNA), a valine amino acid will be produced at the 158th codon of the membrane-bound form. If the sequence has an adenine substitution for guanine, the codon will give rise to methionine. Until recently, many researchers were propagating

reports that, at body temperature, the Valine (Val158) allele produces a version of COMT that is stable and has a four-fold increase in activity beyond that of the more thermolabile Methionine (Met158) variant. However, Shield, Thomae, Eckloff, Wieben, & Weinshilboum (2004) have pointed out that early studies were conducted at erroneous temperatures and that, at true body temperature, the Val158 polymorphism generates a COMT version with two times the activity of the Met158 allele. Nevertheless, individuals with a Val/Val genotype would experience a greater degree of catecholamine inactivation than would individuals with a Met/Met genotype (Weinberger, 2001).

Because there are few dopamine reuptake transporters in the PFC, the termination of dopamine in this region occurs largely due to the enzymatic action of COMT. This is in contrast to the striatum (i.e. caudate and putamen) which, with its abundance of dopamine transporters, terminates the neuromodulator predominantly by reuptake. Evidence for this differential distribution has been demonstrated in numerous studies. *COMT* knockout mice exhibit normal levels of dopamine in the striatum but substantially increased concentrations in the PFC (Gogos et al., 1998). In rodents and humans, it has been found that *COMT* mRNA is predominantly expressed in prefrontal neurons (Matsumoto et al., 2003). Post mortem investigations have similarly suggested that the Val allele is associated with heightened COMT activity in the PFC and consequently decreased levels of prefrontal dopamine (Perlman, Weickert, Akil, & Kleinman, 2004). (Weinberger, 2001; Weinberger, 2005). In both rats and humans, the administration of COMT inhibitors was able to improve performance on a working memory task (Gasparini, Fabrizio, & Bonifati, 1997; Lijequist, Haapalinna, Ahlander, Li, &

Mannisto,1997). These findings seem to support the suggestion that COMT influences the regulation of prefrontal dopamine.

The Role of Dopamine

A large body of accumulated evidence indicates that schizophrenia patients exhibit aberrant physiological activity (i.e. either hyperactivation or hypoactivation) in the PFC while performing tasks that rely upon executive function. Using fMRI, several investigators have reported PFC overactivation in schizophrenia patients who displayed impaired performance during executive tasks of working memory (Callicott et al., 2000; Manoach et al., 1999). This overactivation has been described by Tunbridge, Harrison & Weinberger (2006) as being the result of inefficient prefrontal function, requiring an increased amount of activation for a given degree of performance compared to healthy controls.

Although PFC hyperactivation has been reported, it is PFC hypoactivation that has been particularly, and consistently, associated with schizophrenia patient performance during working memory tasks (Weinberger 2001). It has been suggested that the findings of reduced PFC activity in both non-psychiatric human subjects (Callicott & Weinberger, 1999) as well as non-human primates (Funahashi, Bruce, & Goldman-Rakic, 1989; Funahashi, Bruce, & Goldman-Rakic, 1991) during conditions that consume more than one's available working memory resources, implicates PFC underactivation in schizophrenia patients to be the result of an inability to meet processing demands.

According to Tunbridge et al. (2006), dopamine has an inverted U-shape relationship with PFC activity where intermediate levels of dopamine support a maximally performing PFC and low or high levels of dopamine are associated with compromised PFC operation. In terms of PFC activation, low or high levels of dopamine may be manifested respectively as hypoactivation (insufficient processing) or hyperactivation (inefficient processing). It has been proposed that dopamine regulates PFC activation by modulating the excitatory effects of glutamate as well as the inhibitory effects of local GABA cells (Weinberger, 2001). During working memory performance, dopamine coordinates the firing of pyramidal neurons by potentiating the excitatory action of sustained inputs as well as dampening the signal from transient inputs. In other words, dopamine assists in increasing the signal to noise ratio within contexts involving working memory. Bilder, Volavka, Lachman, & Grace (2004) suggest that the Met158 allele increases the PFC signal to noise ratio and consequently improves the working memory subprocess of maintenance. The authors warn, however, that this maintenance stability may have the effect of weakening the mental flexibility necessary for the working memory subprocess of updating (i.e. monitoring).

Weinberger (1987) contends that prefrontal dopamine underactivation may have the downstream effect of mesolimbic dopamine overactivation. It has been proposed that the high-activity Val allele can have a two-fold effect on dopamine: 1) reduces dopamine signaling in the PFC, and 2) increases it in the mesoencephalic region of the brain (Harrison & Weinberger, 2004). This differential regulatory effect provides a mechanism to account for the observed hypofrontality and putative mesencephalic

hyperdopaminergia in schizophrenia. PFC is generally able to inhibit mesolimbic dopamine using prefrontal projections that use GABA to inhibit mesoencephalic neurons directly or indirectly further upstream at the level of the midbrain. Therefore, *COMT* has the ability to modulate dopamine activity in the PFC as well as in mesoencephalic areas: the low activity Met158 allele can allow for more prefrontal dopamine which consequently inhibits mesolimbic dopamine, while the high activity Val158 allele can reduce PFC dopamine which consequently allows for increased mesolimbic dopamine. The low activity Met158 allele appears to contribute to intermediate PFC dopamine levels and consequently, an optimally performing PFC. The high activity Val158 allele produces reduced PFC dopamine levels which may cause insufficient or inefficient PFC activity.

Other investigators explain the variations of hypo- and hyperactivation as a function of differences in experimental context (Hofer & Weiss, 2002) and task parameters such as cognitive demand, strategy, or motivation (Manoach et al. 1999).

COMT Association Studies

Association studies in schizophrenia attempt to determine if a particular allele is present in the patient group more often than in the non-psychiatric comparison group. Several studies have reported an association between schizophrenia and *COMT* polymorphisms or haplotypes in Chinese (Li et al., 2000), French (De Chaldee et al., 1999), and Jewish (Horowitz, Shifman, Rivlin, Pisante, & Darvasi, 2005; Shifman et al., 2002) populations. With specific regard to *COMT* alleles, findings from association studies involving American (Egan et al., 2001; Wonodi, Stine, Mitchell, Buchanan, &

Thaker, (2003), Palestinian (Kremer et al., 2003), Chinese (Li et al., 1996), Irish (Chen, Wang, O'Neil, Walsh, & Kendler, 2004), and French (De Chaldee et al., 1999) populations, have suggested that the Val allele is associated with schizophrenia. Other investigations involving American (Egan et al., 2001), Candian (Joober et al., 2002), Caucasian and Japanese (Kunugi et al., 1997) as well as Chinese (Fan et al., 2005) participants similarly found Val associated with the psychiatric condition although the finding did not reach significance. Other studies have not found significant association between *COMT* and schizophrenia in Caucasian-American (Ho et al., 2005; Strous, Bark, Woerner, & Lachman, 1997), Indian (Semwal et al., 2001), Chinese (Fan et al., 2002; Tsai, Hong, Liao, Lai, & Liou, 2004), Taiwanese (Chen, et al. 1997; Liou, Tsai, Hong, Wang, & Lai, 2001), Japanese (Inada, Nakamura, Iijima, 2003), Korean (Joo et al., 2005), French (De Chaldee et al., 2001), and Bulgarian (Williams et al., 2005) populations nor in patients from the United Kingdom (Daniels et al., 1996; Wei, & Hemmings, 2000).

Three meta-analyses have examined the results of association studies regarding *COMT* alleles and schizophrenia. The Glatt, Faraone, & Tsuang (2003) study indicated that there was evidence to suggest that the Val158 allele has an association with schizophrenia in European, but not Asian, samples. The Fan et al. (2005) meta-analysis initially indicated that no association was found between the Val158 variant and schizophrenia in European or Asian samples. However, the authors explain that if the Shifman et al. (2002) study on Ashkenazi Jews of European ancestry is included in the analysis, a significant association between Val158 and schizophrenia is revealed for

European samples. In their meta-analysis, Munafo, Bowes, Clark, & Flint (2005) reported that a significant association between the Val158 allele and schizophrenia was found. However, after excluding studies containing controls whose allele frequencies departed from Hardy-Weinberg equilibrium, the association was no longer significant.

Inconsistent findings among association studies of complex diseases like schizophrenia are common for several reasons. Although the likelihood of detecting the susceptibility gene of a simple, single-gene illness is low, in the case of complex, multi-gene diseases, it is less difficult to happen upon one of the genes initially. However, the power of follow up studies to replicate the finding is usually low. The use of small sample sizes yields low statistical power and consequently increases the frequency of false positive and false negative findings as well as failure to replicate. Also, many association studies of schizophrenia have used the case-control approach, which can suffer from false positive results when population stratification occurs as a consequence of inadequately-matched controls. Additionally, the power of molecular genetic studies on schizophrenia has been weakened by the reliance on clinical diagnosis to define the disease phenotype. The power of genetic studies would likely be improved by using larger sample sizes, family-based approaches, and an endophenotype to classify the proband group.

Genotyping Studies of *COMT* Val158Met Polymorphism and Working Memory Function

Numerous investigations have sought to determine if the *COMT* Val158Met polymorphism is associated with neurocognition or prefrontally mediated behavior.

Barnett et al. (2007) reported that, within a large sample of children, better performance on a working memory task that involved recalling the number of dots presented on a computer screen, was associated with greater Met158 allele loading. Diamond, Briand, Fossella, & Gehlbach (2004) found that children with the Met/Met genotype demonstrated better performance on one test sensitive to dorsolateral PFC function (i.e. dots mixed task) but not another (i.e. self-ordered pointing task). Examining healthy volunteers, Malhotra et al. (2002) similarly reported that individuals homozygous for Met produced less perseverative errors on the WCST than those with other genotypes. Assessing healthy adults on a variety of working memory tests, Bilder et al. (2002) reported that the only task that required manipulation (i.e. Letter Number Sequencing) demonstrated genotype differences where those homozygous for Met performed the best while those homozygous for Val were the worst. These authors point out that genotype differences were not found for the Spatial Delayed Response Task, which only requires maintenance, nor for the n-back which places demands on monitoring. It was suggested that higher-order working memory processing like manipulation is more directly related to the *COMT* gene than other working memory subprocesses. Also, Bruder et al. (2005) found that genotype and WCST scores shared variance to generally the same degree as the other studies (i.e. 2%). They reported that the Met allele was associated with better, though nonsignificant, Letter Number Sequencing performance though they did not find any genotype differences on WCST performance. Generally, these various genotyping studies in normal controls appear to provide support for Bilder's suggestion that the

manipulation subprocess of working memory may be more sensitive to *COMT* than the other subprocesses.

The *COMT* Val158Met polymorphism has been studied in schizophrenia patients and their siblings during various working memory tasks. Using an n-back task that places high demands on monitoring, Goldberg et al. (2003) reported that, across groups and conditions, those with the Val/Val genotype were the least accurate, those with Met/Met were the most accurate, and heterozygotes were intermediate. Across conditions, schizophrenia patients were less accurate than both healthy controls and siblings while the siblings trended toward worse accuracy than controls. Woodward, Jayathilake, and Meltzer (2006) reported that among mostly unmedicated schizophrenia patients, Met homozygotes performed better than Val homozygotes on the Auditory Consonant Trigram Test of working memory. Although the authors anticipated that performance of the Met homozygote group would improve after treatment with clozapine, this did not occur. However they suggest that the atypical antipsychotic medication likely raised PFC dopamine to beyond the level of maximal performance along the inverted U-shaped function curve, as described by Tunbridge et al. (2006). On 0-, 1-, and 2-back tasks, Diaz-Asper et al. (2008) reported that Val homozygotes performed worse than heterozygotes or Met homozygotes within their combined sample of schizophrenia patients, relatives of schizophrenia paitents, and nonpsychiatric controls. They also found a main effect of diagnostic group where the patients performed worse than the patients' relatives, who performed worse than the controls. Using a combined score of the WCST perseverative errors and Continuous Performance Test-AX (CPT-

AX) errors, Galderisi et al. (2005) did not find any differences between patients divided by deficit or non-deficit subtypes of schizophrenia. However, they did find that the Val homozygotes performed at levels below that of the participants with other genotypes. They further reported that the *COMT* polymorphism accounted for 6.6% of the variance on these tasks. Egan et al. (2001) similarly found worse WCST performance in Val homozygotes than other genotypes and worse performance among schizophrenia patients and their siblings than in healthy controls. The COMT polymorphism accounted for 4% of the variance for frequency of perseverative errors. As indexed by fMRI activation, Val homozygotes were less efficient than heterozygotes, who were less efficient than Met homozygotes. Furthermore, these authors' association study revealed that the Val allele was transmitted more often to the patients than the Met allele. Joober et al. (2002) reported that the Met homozygotes displayed a trend for less perseveratve errors on the WCST than the other genotypes. This study also indicated a nonsignificant finding of higher Val allele frequency in the schizophrenia patients.

Although the majority of COMT genotyping studies have generally reported disadvantages related to the Val allele, two studies did not find any genotype differences among schizophrenia patients and controls. Although Ho et al. (2005) did observe more PFC activation in Val homozygotes than Met homozygotes during an n-back task, genotype groups did not differ on the WCST or Digit Span Backwards. A study by Minzenberg et al. (2006) that included individuals with schizotypal personality disorder, nonschizotypal personality disorders, and nonpsychiatric controls, found no genotype nor diagnostic group differences on the WCST or a visuospatial working memory task (i.e.

DOT task). Among a sample that combined schizophrenia patients and nonpsychiatric controls, Bosia et al. (2007) found no differences between genotype groups on a digit sequencing working memory task. For these studies with seemingly discrepant findings regarding *COMT* Val158Met genotype, examination of methodology did not reveal any irregularities that could account for the inconsistent results. Generally though, the majority of genotyping studies in schizophrenia patients and their relatives appear to indicate that the Val allele is associated with compromised executive function in a dose-dependent fashion.

Populations at high risk for schizophrenia have been investigated in genotyping studies as well. Rosa et al. (2004) examined a group of schizophrenia spectrum and psychosis patients as well as their relatives. Patients produced more WCST perseverative errors than their siblings. Although no genotype differences were shown for the patient group, in siblings, Val homozygotes performed worse than other genotypes on the WCST. Similarly, while no allele association was detected in the patient group, in the sibling group, the Met allele was found to be associated with less WCST perseverative errors. In young, male volunteers who scored high for self-reported schizotypy symptomatology, Avrampoulus et al. (2002) determined that individuals homozygous for the Val allele produced the highest schizotypal scores. In these various genotyping studies of groups at high risk for schizophrenia, the degree of genetic risk for the disorder was never examined. However, it is interesting that, like the findings for schizophrenia patients and their relatives, it appears that the Val allele is related to deficient executive function in a dose-dependent fashion.

Specificity of *COMT* Val158Met Polymorphism

Schizophrenia and bipolar disorder have historically been characterized as distinct psychiatric illnesses as emphasis has been placed the symptoms that allow them to be differentially diagnosed. Yet, according to Maier, Hofgen, Zobel, & Rietschel (2005), convincing evidence has yet to be provided for justifying the differential taxonomy of these two disorders and recent research evidence is now challenging their distinction (see Berretini et al., 2003 for review). Maier et al. point out that, besides the obvious symptom overlap, both illnesses are associated with enlarged ventricles, diminished hippocampal size, and similar cognitive impairments.

Genetic studies are similarly suggesting overlap in schizophrenia and bipolar disorder. For example, linkage analyses have implicated chromosome 22 in bipolar disorder (Detera-Wadleigh et al., 1999; Edenberg et al., 1997; Mujaheed et al., 2000). Examining families with psychotic mood disorders, Potash et al. (2003) reported linkage to 22q12. With regard specifically to *COMT*, Shifman et al. (2004) revealed an association between bipolar disorder and a COMT haplotype that was previously found to be associated with schizophrenia (Shifman et al., 2002). Meta-analyses have been conducted by several researchers in an attempt to elucidate the specificity of susceptibility loci. Based upon the findings from their meta-analysis, Badner and Gershon (2002) concluded that 22q contains a predisposing locus common to both schizophrenia and bipolar disorder. The authors further propose 22q11 as the foremost candidate region for bipolar disorder. However, a rank-based genome scan meta-analysis examination of 18 bipolar disorder genome scan data sets failed to find a region that

achieved genomewide significance. As evidence has implicated chromosome 22 involvement in bipolar disorder, patients with this psychiatric condition constitute an appealing comparison group for any study examining the specificity of genetic effects in schizophrenia.

It is important to note that of the few genetic studies that have examined *COMT* Val158Met alleles related to bipolar disorder, there are only reports of association with the Met allele (Arias et al., 2006; Lachman et al., 1996; Rotondo et al., 2002). This Met association has been similarly reported in genotyping studies of obsessive-compulsive disorder (Karayiorgou et al., 1997; Karayiorgou et al., 1999), panic disorder (Woo, Yoon, Yu, 2002), and aggression (Rujescu, Giegling, Gietl, Hartmann, & Moller, 2003). Regarding studies of *COMT* alleles in bipolar disorder, only the Met allele has been implicated. This is in stark contrast to the widespread reports of schizophrenia associations with the Val allele. No studies exist which jointly examine the association between the maintenance, monitoring, and manipulation components of working memory performance and *COMT* Val158Met alleles in either bipolar disorder patients or their relatives.

COMT Val158Met Polymorphism Interaction with Other Loci

Research studies have examined working memory with consideration to possible interactions between the *COMT*'s Val158Met polymorphism and: 1) other genes, as well as 2) *COMT*'s other polymorphisms. For example, although Meyer-Lindenberg et al. (2006) found an increased prefrontal inefficiency on a 2-back task for Val158Met heterozygotes and Val homozygotes, than Met homozygotes, they reported that

increasingly stronger associations were associated with increasing inclusion of other *COMT* polymorphism loci. The authors suggest that effects on the PFC of Va158Met allele carriers will vary contingent upon that allele's haplotype relationship with other regions on the *COMT* gene.

Other studies have investigated working memory within the context of the *COMT* Val158Met polymorphism's interaction with other genes. Using fMRI during the n-back task, Tan et al. (2007) found disproportionately inefficient dorsolateral PFC activation when participants carried both the *COMT* Val158 allele and the A allele of a gene for a metabotropic glutamate receptor (i.e GRM3). In contrast, the authors report that the Met158 homozygote genotype reduced the inefficient effects of the GRM3-A allele.

In their genotyping study, Roffman et al. (2008) used a continuous performance task where working memory contents are maintained and scanned (Sternberg Item Recognition Paradigm) to evaluate brain activation of schizophrenia patients and nonpsychiatric controls. Among schizophrenia patients but not controls, the T allele of the *MTHFR* gene's C677T polymorphism was associated with decreased activation of the PFC and insular cortex. Additionally, reduced activation was associated with the 677T and Val158 alleles in schizophrenia patients but 677C and Met158 alleles in controls. According to the authors, the *COMT* and *MTHFR* genes interact wherein the 677T allele produces further PFC deficiency in the Val158 carriers among schizophrenia patients.

On a working memory task of maintenance of phonological and serial word order (Word Serial Position Test), Xu et al. (2007) found that the presence of the C allele for the *DRD2* gene's C957T polymorphism was associated with worse performance than the

T allele among those with a Met/Met genotype for the *COMT* Val158Met polymorphism. Furthermore, no differences were revealed for the n-back or Spatial Delayed Response Task. Although the findings may appear to conflict with other studies regarding the Met158 allele, the authors suggest that the *DRD2* gene likely modifies the effects of the *COMT* gene.

These various results regarding relationships among the *COMT* haplotypes as well as between *COMT* and other genes seem to indicate that the PFC effect of the *COMT* Val158Met genotype may vary depending upon its interactions with other loci.

LITERATURE SUMMARY AND OBJECTIVES OF THE PRESENT INVESTIGATION

It has been posited that the effects of disease genes are more greatly exhibited in cognition than as a clinical symptom profile (Weinberger 2005). Specific neurocognitive performance may serve as an observable reflection of susceptibility genes. Unlike clinical diagnosis, which is generally qualitative, quantitative endophenotypes can take advantage of the power of available statistical analyses. A wide array of research evidence indicates that working memory impairment may reflect heritable liability for schizophrenia and thus is promising as an endophenotype for the illness.

In contrast, very few studies have explored working memory in patients with bipolar disorder; an illness some have claimed may overlap with schizophrenia (Maier, Hofgen, Zobel, & Rietschel, 2005; Berretini, 2003). Even fewer have directly compared bipolar disorder patients' performance to that of schizophrenia patients. It is important to determine whether working memory deficits are specific to schizophrenia or also present in other psychiatric disorders such as bipolar disorder. Determining the specificity of such impairments would provide valuable insight regarding potential similarities or differences in the underlying neuropathology of schizophrenia and bipolar disorder. For example, if equivalent working memory defects are revealed in both schizophrenia and bipolar disorder, the neurodevelopmental theory (Weinberger, 1987) purported in schizophrenia pathophysiology might be extended to bipolar disorder. Extant findings generally suggest that bipolar disorder patients have working memory impairment but not to degree of severity present in schizophrenia. Examination of the maintenance,

monitoring, and manipulation subprocesses of working memory could further elucidate the nature of working memory impairment within these two disorders and consequently provide clues to their pathophysiology. To date, no single study has compared all three working memory subprocesses of maintenance, monitoring, and manipulation in schizophrenia as well as bipolar disorder patient groups.

The first question of interest to the present study regards whether deficits in the working memory subprocesses of maintenance, monitoring, and manipulation are specific to schizophrenia patients or are also present in patients with bipolar disorder. The present study will directly compare the performance of these two patient populations on the Spatial Delayed Response Task (i.e. maintenance), Self-Ordered Pointing (i.e. monitoring), and the Digit Span Backwards as well as Letter Number Sequencing tests (i.e. manipulation). It should be noted that although these tasks predominantly measure their respective subprocess of working memory, there might be some degree of overlap between the subprocesses measured by the tasks. For example, maintenance is a requirement of all of these tasks while the updating component of monitoring is likely present in the manipulation tasks. It should further be recognized that the distraction task present during the Spatial Delayed Response Task involves not only maintenance, but also the higher order requirement of shielding maintained information from the interference.

To determine if working memory function can be a strong endophenotype for schizophrenia, its specificity in relatives must also be explored. Observing a deficit in the nonpsychiatric relatives would suggest that the impairment could serve as an

endophenotype for genetic risk for the disorder. It will be important to determine if the deficit is present in the relatives of both disorders as such would indicate that the compromised working memory ability may reflect an endophenotype common to psychiatric disorders in general. However, detecting the impairment in the relatives of only one of these patient groups would suggest the deficit could serve as an endophenotype for that specific illness' disease genes. Such endophenotypes are the direct product or effect of a particular genotype and can be used as a behavioral indicator of the presence of disease-relevant genes. The statistical power of molecular genetic studies can be increased by the inclusion of relatives who demonstrate an illness endophenotype since doing so would classify sample groups using an approach more objective and reliable than the traditional phenotype of clinical diagnosis. Using working memory impairment to identify nonpenetrant carriers of disease genes could increase the power of genetic linkage studies by recruiting group samples that are more etiologically homogeneous.

The findings from the comparison of the relatives of schizophrenia as well as bipolar disorder patients appear to parallel the findings of studies that have compared the patient groups. However the number of studies is very few. Only one study has directly compared the relatives of bipolar disorder and schizophrenia patients for working memory ability (Keri et al., 2001). On a spatial working memory task, this study found a deficit in the siblings of individuals with schizophrenia when compared with healthy volunteers and siblings of bipolar disorder patients. Until further research is done comparing the relatives of individuals with these two illnesses, the specificity of this

potential endophenotype is uncertain. To date, no single study has been conducted to include the maintenance, monitoring, as well as manipulation subprocesses of working memory to directly compare the relatives of bipolar disorder and schizophrenia patients.

The second question of interest to the present study asks whether impairment in working memory subprocesses exists in the relatives of schizophrenia and bipolar disorder patients. Consequently, the maintenance, monitoring, and manipulation performance of relatives of schizophrenia patients and relatives of bipolar disorder patients will be directly compared.

The finding that schizophrenia patients and their clinically healthy relatives both exhibit impaired executive function indicates that alleles that uniquely impact prefrontal cognition may predispose schizophrenia. Despite various reports of linkage to schizophrenia-relevant chromosome regions, very few association or genotyping studies have been conducted with regard to bipolar disorder. As the *COMT* gene provides a mechanism that accounts for the differential regulation of dopamine observed in schizophrenia, it would be worthwhile to explore whether the Val158 allele demonstrates any associations with bipolar disorder. To date, no single study exists that examines the association between working memory subprocesses of maintenance, monitoring, and manipulation and *COMT* alleles in either bipolar disorder patients or their relatives. Such a study would explore the utility of working memory processes as a way to perhaps distinguish bipolar disorder and schizophrenia and increase understanding regarding the relationships between genotype and phenotype in these illnesses.

The final question to be investigated in the present study regards whether the Val158Met polymorphism of the *COMT* gene is associated with compromised working memory subprocess abilities in schizophrenia and bipolar disorder patients and their relatives. To be examined in the present study is whether subprocess deficits are more common among particular *COMT* genotypes of the Val158Met polymorphism (i.e. Val/Val, Met/Met, or heterozygotes) in nonpsychiatric controls as well as across and within schizophrenia as well as bipolar disorder patient and relative groups. This analysis would also directly assess whether working memory impairments in schizophrenia are endophenotypic consequences of the *COMT* gene.

To further investigate the usefulness of working memory impairment as an endophenotype for schizophrenia disease genes, the present study will additionally conduct side-by-side comparisons of the various subprocesses of working memory in schizophrenia patients and their relatives. To determine if any subprocess defects are specific to schizophrenia, the relatives of both schizophrenia and bipolar disorder patients will be compared.

METHODS

Participants

All participants in this experiment were among the individuals who took part in the Cognitive Deficits and Genetics (CDG) study which took place between the years of 2000 and 2004 and endeavored to examine cognitive, psychophysiological, biological, and behavioral indicators of vulnerability to schizophrenia. All participants gave written informed consent and were compensated for their participation. The CDG study protocol was approved by the Minneapolis Veterans Affairs Medical Center and University of Minnesota Institutional Review Boards and underwent annual reviews of the consent process.

All patients spoke fluent English, were literate, did not have a history of illicit drug dependence, had not recently received electroconvulsive treatment, had not sustained a clinically significant head injury, had never received a diagnosis of mental retardation, and had no history of neurological or systemic disease known to affect central nervous system functioning. All participants were examined for visual acuity using the standard Snellen procedure. If necessary, they wore corrective lenses during testing.

Patients were included in the study if they had a history of psychosis or manic episodes; this was later confirmed based upon a structured interview. Diagnoses were acquired from all patients by completing the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) with a trained doctoral-level clinical psychologist. Based upon information from the interview, current symptomatology was rated using the

Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and the 24-item version of the Brief Psychiatric Rating Scale (BPRS) (Lukoff, Nuechterlein, Ventura, 1986). The medical history record as well self-report information was used to determine medical history and medication status. The interviewer completed the Operational Criteria for Psychotic Illness (OPCRIT) (McGuffin, Farmer, Harvey, 1991) after referring to all available clinical information. The OPCRIT was later completed a second time by a different doctoral-level psychologist and diagnostic differences were resolved during consensus meetings during which OPCRIT items of disagreement were again reviewed.

First-degree biological relatives (i.e. parents, siblings, and adult offspring) of patients were first identified from interviews with patients and, by telephone or written correspondence, invited to participate in the study. Relatives of schizophrenia and bipolar disorder patients were excluded from participation if they did not meet the same general and medical criteria as the patients. The only exception to this was that relatives who had past illicit drug dependence were included since it was of interest to study as many relatives as possible from each family.

Nonpsychiatric control participants were recruited from responses to posted announcements at community libraries, fitness centers, the Minneapolis Veterans Affairs Medical Center, and in newsletters for veterans and fraternal organizations. They were excluded from participation if they had lifetime or family histories of psychotic symptoms, affective disorder, previous diagnosis of substance dependence disorder, or

current diagnosis of substance use, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, American Psychiatric Association, 1994).

A doctoral-level psychologist or trained and supervised research assistant used the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, Spitzer, Gibbon, & Williams, 1996) to measure psychopathology in first-degree relatives and nonpsychiatric controls. The SCID-I was initially performed by telephone and later reviewed and confirmed in-person with a doctoral-level psychologist or a trained, advanced graduate student who had no knowledge of the diagnosis. Nonpsychiatric controls and relatives were assessed with the Structured Clinical Interview for DSM-IV Axis I Personality Disorders Personality Questionnaire (SCID-II-PQ) (Ekselius, Lindstrom, von Knorring, Bodlund, & Kullgren, 1994). After reviewing the SCID-II-PQ responses, the interviewer completed further inquiries using the necessary sections of the SCID-II Interview (First, 1997). The interviewer used the Structured Interview for Schizotypy (SIS) (Kendler, Lieberman, & Walsh, 1989) to acquire ratings for schizotypal, schizoid, and paranoid personality disorders. A consensus procedure that adhered to the guidelines of Leckman and colleagues (Leckman, Sholomskas, Thompson, Belanger, Weissman, 1982) was completed to acquire lifetime Axis I and II diagnosis status in relatives and controls. This process was performed by a doctoral-level psychologist or trained, advanced graduate student who reviewed the SCID-I, SCID-II, SIS, medical history, and family informant information. Control and first-degree biological relatives of patients were assessed for schizotypal symptomatology using the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991). Intelligence quotients were

derived using a short form assessment consisting of the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) (Psychological Corporation, 1997). It has been demonstrated that the combination of the Vocabulary and Block Design subtests of the WAIS-III results in a short form assessment that can be used to provide gross estimates of Full Scale IQ (Ringe, Saine, Lacritz, Hynan, & Cullum, 2002). Jeyakumar, Warriner, Raval, and Ahmad (2004) found that this dyadic combination of Vocabulary and Block Design WAIS-III subtests results in a valid and reliable estimate of IQ.

Assessment of Working Memory Subprocesses

To measure the working memory subprocess of maintenance, a computerized visual-manual version of the Spatial Delayed Response Task was administered. Each participant was seated in a quiet, dimmed room and seated before a computer monitor where her/his eyes were 23.5 cm from the computer monitor. Participants were advised to remain still and were observed by the experimenter who ensured participants' heads did not move. At the beginning of each trial, the participant fixated on a small, black asterisk in the center of the monitor screen. After 2 seconds, a target stimulus was briefly presented at one of 16 possible locations that were equidistant in a circle configuration 4.5 cm from the fixation. A small black dot was used as the target stimulus. The participant was instructed to mark the position of the target stimulus by using a light pen to touch that position location on the monitor screen.

Three conditions were presented, each varying in either the duration of time the participant had to wait before making their response or the type of interference presented

during the delay duration. Before actual testing in each of the three conditions, practice trials were completed by the participant to verify comprehension of the task instructions.

The three experimental conditions employed wherein the target was briefly presented for 200 msec were .5 sec delay, 6 sec delay involving a verbal semantic categorization interference task, and 6 sec delay involving a spatial interference task. After the target flash, the screen would darken for the delay period, and its later lightening would cue the participant to make her/his response. The conditions of delay with interference served to ensure that participants were not cheating by holding their gaze at the to-be-remembered target location. During the condition requiring the delay with verbal interference task, the target stimulus (i.e. small black dot) would disappear followed by the serial presentation of various words, only one of which was not consistent with the semantic category that the rest of the words belonged to. This delay period ended with the participant audibly stating the word that was inconsistent with the semantic category.

During the condition requiring the delay with spatial interference, the disappearance of the target stimulus was followed by the presentation of a circle with a line through it. At this point, the participant had already been instructed to remain visually focused on the initial fixation asterisk. After the appearance of the circle and line, a second asterisk was presented and the participant was required to audibly indicate if the second asterisk had been located higher than or lower than the circle and line.

For every trial, the distance between the target location and the response location was calculated and transformed into an error score in mm. There were sixteen .5 sec

delay trials, sixteen 6 sec delay with verbal interference trials, and sixteen 6 sec delay with spatial interference trials.

The monitoring subprocess of working memory was assessed by administering the computerized Self Ordered Pointing task from the Curtis, Zald, and Pardo (2000) study which was modeled after Petrides and Milner (1982). For this task, participants were seated in a quiet, dimmed room with their head stabilized by a chinrest that positioned their eyes 27 cm from the computer monitor. For the task, 11 geometric line drawings of objects were displayed in a 3 x 4 array and the participant was instructed to use the light-pen to select, in any order, an object only once. The objects were designed and drawn to be unusual items that did not resemble existing real-world objects which were easily named. Participants were instructed to avoid choosing the same object more than once. After each time the participant made a selection, the objects were randomly rearranged within the presentation matrix and this also served as a cue to initiate the next selection. The end of the task occurred when all objects had been chosen or when 30 trials had been given, whichever happened first. To prevent participants from using the randomization of object presentation to their advantage by selecting objects exclusively from one location in the matrix, a black square would overlap the location of the most recent response and would not accept selection for the upcoming trial. After completion of the task, the number of trials necessary to complete the task was calculated.

The Digit Span Backwards task of the WAIS-III was used to assess a low-demand manipulation subprocess of working memory. For this task, the participant had to recite in reverse order, a series of digits immediately after the series was presented at a rate of

one per second. Each trial consisted of an increasingly longer series until the participant consecutively failed three trials of the same length**.** The maximum number of digits correctly recalled in a series was recorded.

To examine a high-demand manipulation subprocess of working memory, the Letter Number Sequencing task from the WAIS-III was administered. For each trial, a series of alternating letters and numbers were read to the participant at a rate of one per second. To respond, the participant was to recall aloud, first the numbers in ascending order, and then the letters in alphabetical order. The number of items increases by one until the participant consecutively fails three trials of the same series length. After the task, the number of items of in the longest series of correctly-recalled items is calculated. According to Conklin et al. (2005), since the Digit Span Backwards only requires alphabetizing of letters while the Letter Number Sequencing task involves both alphabetizing as well as numerical ordering, the former places low demands on manipulation while the latter requires a higher degree of manipulation processing.

Genotyping

We determined the *COMT* Val 108/158 Met genotype for each individual by a restriction fragment length polymorphism technique. Whole blood was collected on Whatman FTA Matrix specimen collection cards. Punches from the FTA blood cards were then prepared for PCR analysis according to Whatman FTA protocol. The washed punch was used directly for PCR amplification (single nucleotide polymorphism rs4680) (forward primer 5' tactgtggctactcagctgtgc 3;: reverse primer 5'gtgaactggtgtgaacacc 3'). Amplification was carried out as described by Bergman-Jungestrom and Wingren

(Bergman-Jungestrom & Wingren, 2001). PCR reactions were initially denatured at 94 degrees Celsius for 3 minutes followed by 39 cycles of denaturation at 93 degrees for 45 seconds and annealing at 55 degrees for 1 minute and extension at 72 degrees for 1 minute with a final 4 minute extension at 72 degrees. The PCR products were digested with *Nla* III (New England Biolabs) for 3 hours at 37 degrees followed by incubation at 60 degrees for 20 minutes to denature the enzyme. The digestion was then separated by polyacrylamide gel electrophoresis and the digestion products visualized by staining with ethidium bromide. The *COMT* Val allele has a G at position 1947 yielding a 114 base pair fragment after digestion with *Nla* III whereas the *COMT* Met allele has an A at this position which allows digestion of the 114 base pair fragment into two products of 96 and 18 base pairs. The entire sample of participants was in Hardy Weinberg equilibrium, X^2 = (1, $\underline{n}$=216) = .66, $\underline{p}$=.41.

RESULTS

Comparison of Patient Diagnostic Groups on Individual Tasks

Normality

The working memory performance of schizophrenia patients, bipolar disorder patients, and nonpsychiatric controls were compared to investigate specificity of impairment on this cognitive function. Before conducting parametric tests on the group data for working memory performance, distribution graphs and results from tests of normality, skewness, and kurtosis were first examined. Although the tests of normality (i.e. Shapiro-Wilk's W) indicated non-normal distribution of data, the appropriateness of parametric analyses was ensured by a lack of any significant skewness or kurtosis. This was confirmed by considering the reasonability of scores in the distributions and finding Fisher's Kurtosis scores and SPSS skewness scores that were below 2 or above -2; limits deemed generally acceptable (George & Mallery, 2001). Levene's Tests for homogeneity of variance were conducted on the data for each working memory task. Only the Digit Span Backwards demonstrated a lack of equal variances between the groups and therefore for any relevant t-tests, the output for unequal variances will be referenced.

Demographics

Table 1 summarizes the demographic characteristics of the nonpsychiatric control group as well as the patient groups. Since age differences were found among the original sample of patients and nonpsychiatric controls in this analysis, the groups were made more similar by limiting participants to those older than 23 years and younger than 65.

With this modified age range, an One Way Univariate ANOVA indicated no group differences for age (F=1.69, df=2,153, p=.19). A Chi Square indicated that there was no difference between patient groups in their proportions of ethnic groups $X^2(3, n=84)=4.16$, p=.24. For the respective schizophrenia as well as bipolar disorder patient groups, the percentages within each ethnic group were as follows: Anglo Saxon 85.5% and 96.6%, Eastern European 5.5% and 0%, Native American 1.8% and 3.4%, and African American 7.3% and 0%.

A Chi Square test revealed a significant difference between the proportions of males and females for these groups**,** X^2 (2, n=156) = 14.4, p=.001). To avoid any confounds that could be attributed to differences in gender composition, gender was made a between-subjects factor in all tests of patients' working memory performance.

An One Way Univariate ANOVA (F=4.65, df=2,153, p=.01) revealed that the nonpsychiatric controls (p=.003) had more years of education than the schizophrenia patients. The bipolar disorder patients showed a similar trend (p=.08) for more education than schizophrenia patients. However, ANCOVAs were not performed using Education as a covariate since there was a concern that statistical correction of the shared variance between Education and working memory performance would obscure a genuine group effect. It has been argued that statistically controlling for nuisance variables, like Education, would be misleading as it could reduce the effects of disease genes that are responsible for both working memory performance and the schizophrenia diagnosis (Meehl, 1971).

Intelligence quotients were determined using the short form combination of the Vocabulary and Block Design subtests of the WAIS-III. An One Way Univariate ANOVA (F=16.5, df=2,152, p<.0005) on IQ score indicated that schizophrenia patients had lower IQ scores than bipolar disorder patients (p<.0005) as well as nonpsychiatric controls (p<.0005). Pearson Product Moment Correlations collapsed across all participant groups indicated that performance on the spatial interference condition of Spatial Delayed Response Task (r=-.31, df=108, p=.001), verbal interference condition of Spatial Delayed Response Task (r=-.30, df=108, p=.001), sensorimotor control condition of Spatial Delayed Response Task (r=-.21, df=108, p=.03), Self Ordered Pointing (r=-.27, df=141, p=.001), Digit Span Backwards (r=.47, df=153, p<.0005), and Letter Number Sequencing (r=.44, df=149, p<.0005) were significantly correlated with IQ. Just as educational performance and persistence is likely impacted by working memory ability, there is concern this same cognitive process influences IQ. Statistically controlling for IQ could reduce the effects of disease genes responsible for both working memory performance and the schizophrenia diagnosis. Although ANCOVAs with IQ as a covariate will be provided as a supplement to the standard ANOVAs, the interpretive focus will be on the results of the standard ANOVAs.

To evaluate whether antipsychotic medication was influencing cognitive function, Pearson Product Moment Correlations examined for an association between chlorpromazine (CPZ) equivalents and the performance of schizophrenia as well as bipolar disorder patients on each working memory task. The lack of relationship for the spatial interference condition of the Spatial Delayed Response Task (r=.03, df=59,

p=.82), verbal interference condition of the Spatial Delayed Response Task (r=-.03, df=59, p=.82), Self Ordered Pointing task (r=.09, df=59, p=.46), Digit Span Backward task (r=-.09, df=59, p=.49), and Letter Number Sequencing task (r=-.03, df=59, p=.84) ensured that any group differences on working memory performance cannot be due to antipsychotic medication differences between patients.

Working Memory Performance

To probe the maintenance subprocess of working memory, a Two Way Repeated Measures ANOVA was performed on Spatial Delayed Response Task performance where Diagnostic Group (Nonpsychiatric Controls, Schizophrenia Patients, and Bipolar Disorder Patients) and Gender (Male and Female) were between-subjects factors while Type of Interference (Spatial and Verbal) was the within-subjects factor. Although there was no main effect for Gender (F=.19, df=1,105, p=.66, η^2=.002), there was a main effect revealed for Diagnostic Group (F=4.19 df=2,105, p = .01, η^2=.074). A follow up One Way ANOVA comparing diagnostic groups collapsed across both interference conditions was conducted and Figure 1 shows the main effect of Diagnostic Group (F=4.36, df=2,108, p=.01, η^2=.075) where the schizophrenia patients (M=15.03, SD=5.17, n=39) were significantly less accurate than nonpsychiatric controls (M=12.07, SD=4.12, n=43, p=.004) in spatial working memory across both types of interference conditions. Although bipolar disorder patients (M=13.09, SD=4.34, n=29, p=.36) did not differ from nonpsychiatric controls, there was a trend where the bipolar disorder patients were more accurate than the schizophrenia patients (p=.09). Additionally, Figure 2 shows there was a main effect for Type of Interference (Greenhouse-Geisser, F=13.37, df=1,105, p<.0005,

η^2=.117) where spatial interference (M=14.32, SD=6.00) produced greater impairment than verbal interference (M=12.35, SD=4.41) in participant accuracy. There were no Gender X Type of Interference (Greenhouse-Geisser, F=.02, df=1,105,p=.89, η^2=.000), Diagnostic Group X Gender (F=.27, df=2,105,p=.76, η^2=.005), Diagnostic Group X Type of Interference (Greenhouse-Geisser, F=2.43, df=2,104, p=.09), nor Diagnostic Group X Gender X Type of Interference interactions (Greenhouse-Geisser, F=1.15, df=2,105, p=.32, η^2=.021).[1] An ANCOVA with IQ as covariate found no main effect for Diagnostic Group (F=1.87, df=2, 106, p=.16, η^2=.034), no main effect for Type of Interference (F=1.02, df=1, 106, p=.31, η^2=.010), and no Diagnostic Group X Type of Interference interaction (F=1.06, df=2, 106, p=.35, η^2=.020).

The results of the standard ANOVAs on the Spatial Delayed Response Task appear to indicate that schizophrenia patients are less able than nonpsychiatric controls at maintaining information in working memory. The findings also suggest that spatial interference impaired performance on the task more than verbal interference.

To explore the monitoring subprocess of working memory, a Two Way Univariate ANOVA was conducted on Self Ordered Pointing task performance where

[1] An One Way ANOVA on the Spatial Delayed Response Task's sensorimotor control condition showed a trend for a difference between Diagnostic Groups in accuracy (F=2.59, df=2,108, p=.08) where the schizophrenia patients (M=6.97, SD=2.57, n=39) were less accurate than the nonpsychiatric controls (M=5.94, SD=2.08, n=43, p=.03). The bipolar disorder patients (M=6.11, SD=1.54, n=29) differed in performance from neither the nonpsychiatric controls (p=.75) nor the schizophrenia patients (p=.10). The trend for a difference between the nonpsychiatric controls and the schizophrenia patients was lost after an ANCOVA with IQ as a covariate (F=.90, df=2,102, p=.41). Since only a trend was revealed, these results ultimately indicate that the groups failed to have significant differences in perceptual performance and motor control during the Spatial Delayed Response Task.

Diagnostic Group and Gender were between-subjects factors. There was no main effect found for Diagnostic Group (F=1.98, df=2,138, p=.14, η^2=.03) nor Gender (F=.87, df=1,138, p=.35, η^2=.006). Additionally, there was no Diagnostic Group X Gender interaction (F=.12, df=2,138, p=.89, η^2=.002). The findings of a lack of performance differences between any of the diagnostic groups seems to indicate that bipolar disorder and schizophrenia patients do not differ from nonpsychiatric controls or each other in the working memory subprocess of monitoring.

To investigate a low-demand manipulation subprocess of working memory, a Two Way Univariate ANOVA was conducted on Digit Span Backward task performance where Diagnostic Group and Gender were between-subjects factors. Figure 3 shows the main effect for Diagnostic Group (F=7.84, df=2,149, p=.001, η^2=.09) where the schizophrenia patients (M=4.49, SD=1.04, n=59) recalled significantly shorter strings of reversed number stimuli than nonpsychiatric controls (M=5.54, SD=1.48, n=65, p<.0005) as well as bipolar disorder patients (M=5.48, SD=1.50, n=31, p<.001). Bipolar disorder patients did not differ from nonpsychiatric controls (p=.85). There was no main effect for Gender (F=1.06, df=1,149, p=.30, η^2=.007) and no Diagnostic Group X Gender interaction (F=.08, df=2,149, p=.92, η^2=.001). The main effect of Diagnostic Group remained (F=3.03, df=2,151, p=.05, η^2=.04) after conducting an ANCOVA with IQ as a covariate. These results suggest that a task requiring a low level of working memory manipulation is able to reveal a difference between the psychiatric groups where schizophrenia patients have impaired ability for the working memory subprocess of manipulation compared to bipolar disorder patients and nonpsychiatric controls.

To examine a high-demand manipulation subprocess of working memory, a Two Way Univariate ANOVA was done on Letter Number Sequencing task performance where Diagnostic Group and Gender were between-subjects factors. Figure 4 shows the main effect of Diagnostic Group (F=6.86, df=2,146, p=.001, η^2=.09) where schizophrenia patients (M=4.71, SD=.94, n=55) sequenced and reported significantly shorter strings of alphabetic and numeric items than nonpsychiatric controls (M=5.59, SD=.98, n=66, p<.0005) and bipolar disorder patients (M=5.32, SD=1.17, n=31, p=.007). Bipolar disorder patients and nonpsychiatric controls (p=.22) did not differ from each other. The main effect of Diagnostic Group remained after performing an ANCOVA with IQ as a covariate (F=5.41, df=2,147, p<.005, η^2=.07). There was no main effect for Gender (F=1.27, df=1,146, p=.26, η^2=.009) and no Diagnostic Group X Gender interaction (F=.10, df=2,145, p=.90, η^2=.001). These results seem to confirm that schizophrenia patients demonstrate a detectable deficit in high-demand manipulation performance which isn't present in nonpsychiatric controls or bipolar disorder patients.

After comparing the diagnostic groups on a variety of tasks that focus on different types of working memory, the findings suggest that the maintenance and manipulation subprocesess of working memory are compromised specifically in schizophrenia patients and can possibly serve as a cognitive marker that distinguishes it from bipolar disorder.

Comparison of Relative Groups on Individual Tasks

Normality

The working memory performance of nonpsychiatric controls, relatives of schizophrenia patients, and relatives of bipolar disorder patients were compared to

investigate the utility of working memory impairment as a possible endophenotype for genetic risk to schizophrenia or bipolar disorder. Before conducting parametric tests on the group data for working memory performance, distribution graphs and results from tests of normality, skewness, and kurtosis were first examined. Although the tests of normality (i.e. Shapiro-Wilk's W) indicated non-normal distribution of data, the appropriateness of parametric analyses was ensured by a lack of any significant skewness or kurtosis. This was confirmed by considering the reasonability of scores in the distributions and finding Fisher's Kurtosis scores and SPSS skewness scores that were below 2 or above -2; limits deemed generally acceptable (George & Mallery, 2001). Levene's Tests for homogeneity of variance were conducted on the data for each working memory task. Only the Digit Span Backwards demonstrated a lack of equal variances between the groups and therefore for any relevant t-tests, the output for unequal variances will be referenced.

Demographics

Table 2 summarizes the demographic characteristics of the nonpsychiatric control group as well as the groups of patients' relatives. Since age differences were found for the original sample of patients' relatives and nonpsychiatric controls in this analysis, the groups were made more similar by limiting participants to those older than 24 years and younger than 68. With this modified age range, an One Way ANOVA for Age indicated no significant difference between the groups ($\underline{F}$=1.87, $\underline{df}$=2,168, $\underline{p}$=.16). A Chi Square indicated that there was no difference between relative groups in their proportions of ethnic groups $X^2(4, \underline{n}=103)=6.67$, $\underline{p}$=.15. For the relatives of schizophrenia patients as

well as relatives of bipolar disorder patients, respective percentages in each ethnic group were as follows: Anglo Saxon 94.6% and 93.1%, Eastern European 0% and 3.4%, Russian 0% and 3.4%, Mexican Hispanic 1.4% and 0%, and African American 4.1% and 0%.

A Chi Square indicated that were was no significant difference between the groups in the proportion of males and females; group membership and gender appear to be independent of each other, $X^2(2, n=170)=1.72$, $p=.42$. However, Faraone et al., (1999) have previously reported Diagnostic Group x Gender interactions with regard to performance on tasks of verbal as well as visual memory. Specifically, it was found that, among the nonpsychotic relatives of schizophrenia patients, the performance deficit of the female relatives as compared to females controls, was worse than the performance deficit of the male relatives as compared to male controls. In consideration of the potential association between gender and memory, statistical tests included gender as a between-subjects factor in the analysis of relatives' data to account for any gender effects.

An One Way ANOVA for IQ did not reveal significant differences between the groups ($F=1.73$, $df=2,166$, $p=.18$). An One Way ANOVA for Years of Education revealed a trend where the patients' relatives ($F=2.91$, $df=2,166$, $p=.06$) had less years of education than nonpsychiatric control participants. Paired comparison tests showed that the control participants had more years of education than the relatives of bipolar disorder patients ($p=.03$) and indicated a trend for more years of education than the relatives of schizophrenia patients ($p= .08$).

Working Memory Performance

For the Delayed Response Task, a Two Way Repeated Measures ANOVA was performed with Diagnostic Group (Nonpsychiatric Controls, Relatives of Schizophrenia Patients, and Relatives of Bipolar Disorder Patients) and Gender (Male and Female) as between-subjects factors while Type of Interference (Spatial and Verbal) was the within-subjects factor. There was a trend for a main effect of Diagnostic Group (F=2.57, df=2,133, p=.08, η^2=.037). Figure 5 shows that the relatives of schizophrenia patients (M=13.68, SD=3.69, n=66, p=.02) demonstrated less accuracy in maintenance of spatial information than nonpsychiatric controls (M=12.01, SD=4.1, n=47). See Table 3 for comparisons of means and standard deviations for each diagnostic group. The relatives of bipolar disorder patients (M=12.72, SD=2.99, n=26) did not differ from either the nonpsychiatric controls (p=.44) or the relatives of schizophrenia patients (p=.26). To confirm the effect trend of Relative Group while controlling for any dependencies of Family Membership, a mixed model ANOVA with a fixed factor of Relative Group and random factor of Family Membership was conducted on the Spatial Delayed Response Task data for relatives of schizophrenia patients (Wald Z=.375, p=.71). The results of the mixed model ANOVA (t=-2.41, df=65, p=.02) confirmed the trend that the relatives of schizophrenia patients (M=13.76, SE=.48) were less accurate than the nonpsychiatric controls (M=12.00, SE=.73). Family membership was very weakly associated with Spatial Delayed Response Task performance as reflected by an intraclass correlation of .07 between these two factors. Although there was no main effect of Gender (F=.28 df=1,133, p=.59, η^2=.002), there was a main effect for Type of Interference (Greenhouse-

Geisser, F=23.45, df=1,133, p<.0005, η^2=.15) where spatial interference (M= 13.81, SD=4.55) created greater impairment than the verbal interference (M= 12.07, SD=3.74). A follow up t-test (t=-5.75, df=138, p<.0005) confirmed that the spatial interference condition produced greater impairment in accuracy than the verbal interference condition. Although there was no Diagnostic Group X Type of Interference (Greenhouse-Geisser, F=1.38, df=2,133, p=.25, η^2=.02) nor Diagnostic Group X Gender (F=.55, df=2,133, p=.58, η^2=.008) interaction, there was a significant interaction between Type of Interference and Gender (Greenhouse-Geisser, F=4.90, df=1,133, p=.03, η^2=.036) where females showed significantly greater impairment in accuracy when presented with interference that contained spatial stimuli (M=14.1, SE=.60) rather than verbal stimuli (M= 11.81, SE=.50). For males, there was no difference between accuracy during spatial (M=13.02, SE=.56) and verbal (M=12.17, SE=.47) interference conditions.[2]

These Spatial Delayed Response Task results for patients' relatives groups share some similarity to the results reported for the patients groups. Similar to the maintenance deficit exhibited by schizophrenia patients, findings of the standard ANOVA showed a trend for a maintenance deficit among the relatives of schizophrenia patients. Specifically, the results showed that relatives of schizophrenia patients had a trend for less accuracy than the nonpsychiatric controls. Also, the results of the mixed model ANOVA suggest that when variance due to family membership is controlled for, the difference trend between relatives of schizophrenia patients and nonpsychiatric controls

[2] An One Way ANOVA on the Spatial Delayed Response Task's sensorimotor control condition showed no difference between Diagnostic Groups in accuracy (F=.35, df=2, 136, p=.70, η^2=.005).

remained. Once again, findings show that when a spatial working memory task uses spatial stimuli as the delay period interference, it causes greater maintenance impairment than verbal stimuli. Lastly, findings showed a Gender X Type of Interference interaction where, for females, the performance during spatial interference is worse than the verbal interference.

On the Self Ordered Pointing task, a Two Way Univariate ANOVA did not indicate a main effect for Diagnostic Group (F=1.89, df=2,147, p=.15, η^2=.025) or Gender (F=.09, df=1,147, p=.77, η^2=.001), and did not show a Diagnostic Group X Gender interaction (F=.50, df=2,147, p=.60, η^2=.007). These findings on Self Ordered Pointing resonate the same lack of group differences seen in the analysis on the patient and nonpsychiatric control groups.

For the Digit Span Backwards, Figure 6 shows the Two Way Univariate ANOVA's main effect of Diagnostic Group (F=4.77, df=2,159, p=.01, η^2=.057) where the relatives of schizophrenia patients (M=4.76, SD=1.09, n=71, p=.002) recalled less reversed number stimuli than nonpsychiatric controls (M=5.46, SD=1.49, n=68). Relatives of bipolar disorder patients (M=5.04, SD=1.22, n=26) did not differ from nonpsychitatric controls (p=.16) or relatives of schizophrenia patients (p=.35). However, there was no Gender main effect (F=1.48, df=1,159, p=.32, η^2=.006) nor Diagnostic Group X Gender interaction (F=.005, df=2,159, p=.99, η^2=.000). These findings appear to mirror those seen earlier for the schizophrenia patients in that the relatives of schizophrenia patients similarly show impairment on a task that requires a low level of working memory manipulation. Also, to further examine the effect of Relative Group

while controlling for any dependencies of Family Membership, a mixed model ANOVA with a fixed factor of Relative Group and random factor of Family Membership was conducted on the Digit Span Backwards data for relatives of schizophrenia patients. Family Membership explained a significant amount of covariance (Wald Z=2.41, p=.016). Nevertheless, mixed model results (t=2.85, df=88, p=.005) confirmed the difference between relatives of schizophrenia patients (M=4.74, SE=.19) and nonpsychiatric controls (M=5.45, SE=.25) and an intraclass correlation of .42 suggested that the performance of relatives of schizophrenia patients was moderately affected by studying individuals from the same family.

For the Letter Number Sequencing Task, Figure 7 shows the Two Way Univariate ANOVA's main effect for Diagnostic Group (F=3.69, df=2,159, p=.03, η^2=.044) where the relatives of schizophrenia patients (M=5.10, SD=1.16, n=70, p=.006) sequenced and reported less items than the nonpsychiatric controls (M=5.59, SD=.96, n=69). The relatives of bipolar disorder patients (M=5.27, SD= .92, n=26) did not differ from nonpsychiatric controls (p=.17) or relatives of schizophrenia patients (p=.48). However, there was no Gender main effect (F=.67, df=1,159, p=.41, η^2=.004) nor Diagnostic Group X Gender interaction (F=2.23, df=2,159, p=.10, η^2=.029). Once again, these findings suggest that the relatives of schizophrenia patients, like the schizophrenia patients, show impairment on a task that requires a high level of working memory manipulation. However, to further examine the effect of Relative Group while controlling for any dependencies of Family Membership, a mixed model ANOVA with a fixed factor of Relative Group and random factor of Family Membership was conducted

on the Letter Number Sequencing data for relatives of schizophrenia patients. Family Membership explained a significant amount of covariance (Wald Z=3.032, p=.002). Nevertheless, mixed model results (t=2.33, df=106, p=.02) uphold the difference between relatives of schizophrenia patients (M=5.14, SE=.15) and nonpsychiatric controls (M=5.61, SE=.19) and an intraclass correlation of .43 suggested that Family Membership did exert moderate effects on the performance of relatives of schizophrenia patients. The overall results of the standard ANOVAs for the working memory performance of relatives of patients bear a striking similarity to the results seen for the patients. Just as schizophrenia patients exhibited maintenance and manipulation deficits not present in bipolar disorder patients, the relatives of schizophrenia patients also demonstrate a manipulation deficit and trend for maintenance deficit not seen in relatives of bipolar disorder patients. These findings provide support for the use of maintenance and manipulation as endophenotypes for disease genes associated with schizophrenia per se, rather than psychiatric disorders in general.

Comparison of Genotype Groups on Individual Tasks (Includes All Groups)

Normality

To assess possible cognitive differences among genotype groups of the *COMT* Val158Met polymorphism, genotype groups' performance was compared using a sample that included the nonpsychiatric controls as well as all patient and relative groups. Before conducting parametric tests on the group data for working memory performance, distribution graphs and results from tests of normality, skewness, and kurtosis were first examined. Although the tests of normality (i.e. Shapiro-Wilk's W) indicated non-normal

distribution of data, the appropriateness of parametric analyses was ensured by a lack of any significant skewness or kurtosis. This was confirmed by considering the reasonability of scores in the distributions and finding Fisher's Kurtosis scores and SPSS skewness scores that were below 2 or above -2; limits deemed generally acceptable (George & Mallery, 2001). Levene's Tests for homogeneity of variance were conducted on the data for each working memory task. Only the Digit Span Backwards and Spatial Interference condition of the Spatial Delayed Response Task demonstrated a lack of equal variances between the groups and therefore for any relevant t-tests, the output for unequal variances will be referenced.

Demographics

Table 4 summarizes the demographic characteristics of each Genotype Group. The genotype group samples included participants older than 22 and younger than 68. One Way Univariate ANOVAs for Age (F=.09, df=2,213, p=.91), Years of Education (F=2.16, df=2,212, p=.11), and IQ (F=1.05, df=2,213, p=.35) indicated no difference between the genotype groups. A Chi Square indicated that there was no difference between genotype groups in their proportions of ethnic groups $X^2(24, n=209)=28.27$, p=.25. See Table 5 for the percentages of each ethnicity in each group. A Chi Square indicated there was no difference between the observed and expected numbers of males and females in these Genotype Groups, $X^2(12, n=209)=20.54$, p=.06.

Working Memory Performance

Although an One Way Repeated Measures ANOVA for Spatial Delayed Response Task did not show a Genotype Group effect (F=.88, df=2,179, p=.41, η^2=.010),

there was a main effect for Type of Interference (Greenhouse-Geisser, F=30.35, df=1,179, p<.0005, η^2=.145). As seen throughout earlier analyses, a follow up t-test (t=6.14, df=181, p<.0005) indicated that the spatial interference (M=14.44, SD=5.34) produced greater impairment than the verbal interference (M=12.49, SD=3.92). There was no Genotype Group X Type of Interference interaction (Greenhouse-Geisser, F=1.46, df=2,179, p=.24, η^2=.016). One Way Univariate ANOVAs for the remaining tasks of Self Ordered Pointing (F=.23, df=2,188, p=.80, η^2=.002), Digit Span Backwards (F=.43, df=2,210, p=.65, η^2=.004), and Letter Number Sequencing (F=1.42, df=2,205, p=.24, η^2=.014) did not reveal differences between the Genotype Groups. Although we compared each genotype group on the battery of working memory tasks, there was a surprising lack of effect of *COMT* genotype. [3]

Comparison of Genotype Groups and Patient Groups on Individual Tasks (Includes Patient Groups Only)

Working Memory Performance

To understand if variation in the genotypes would be associated with variation in working memory performance within the groups, genotype groups and diagnostic groups were first investigated among the patient samples. These samples included participants older than 22 years and younger than 68 years. A Chi Square indicated that there was no difference between genotype groups in their proportions of ethnic groups X^2(3, n=82)=4.11, p=.25. For schizophrenia as well as bipolar disorder patients, the respective percentages of ethnicity for each group were as follows: Anglo Saxon 85.2% and 96.4%,

[3] Mixed model ANOVAs were not pursued since there were no significant effects to consider with respect to variance attributable to family membership.

Eastern European 5.6% and 0%, Native American 1.9% and 3.6%, and African American 7.4% and 0%.

A Two Way Repeated Measures ANOVA for the Spatial Delayed Response Task was conducted using Diagnostic Group (Schizophrenia Patients and Bipolar Disorder Patients) and Genotype Group (Val/Val, Heterozygotes, and Met/Met) as between-subjects factors and Type of Interference (Spatial and Verbal) as the within-subjects factor. Although the ANOVA did not show a Diagnostic Group X Genotype Group interaction (F=1.00, df=2,60, p=.37, η^2=.032), it did reveal a trend for a Diagnostic Group X Genotype Group X Type of Interference interaction (F=2.76, df=2,60, p=.07, η^2=.084). To compare Genotype Groups within each patient group, follow up One Way Repeated Measures ANOVAs were separately performed for first schizophrenia patients, then bipolar disorder patients.[4] For schizophrenia patients, there was no main effect of Genotype Group (F=2.03, df=2,35, p=.15, η^2=.10) and no Genotype Group X Type of

[4] The three way interaction was also explored by examining spatial and verbal interference condition scores separately in follow up One Way ANOVAs comparing patient groups within each Genotype Group. For Val homozygotes, a follow up One Way Univariate ANOVA was conducted to compare spatial interference condition performance between patient groups. Figure 8 shows the main effect (F=5.10, df=1,20, p=.03) of Diagnostic Group where the schizophrenia patients with a Val/Val genotype (M=18.07, SD=6.1, p=6.1, n=15) were less accurate than bipolar disorder patients with the same alleles (M=12.64, SD=2.3, n=7). Follow up One Way ANOVAs comparing spatial interference condition performance of patient groups showed no main effects when restricted to only Met homozygotes (F=2.45, df=1,14, p=.14) or Heterozygotes (F=.03, df=1,26, p=.86). Follow up One Way ANOVA similarly comparing verbal interference condition performance of patient groups showed no main effects for Val homozygotes (F=.46, df=1,20, p=.50), Met homozygotes (F=1.07, df=1,14, p=.32), or Heterzygotes (F=1.37, df=1,26, p=.25). The three way Diagnostic Group X Genotype Group X Type of Interference interaction indicates that among Val homozygotes, spatial interference more greatly impaired the schizophrenia patients than bipolar patients on accuracy.

Interference interaction (F=1.75, df=2,35, p=.19, η^2=.091). For bipolar disorder patients, there was no main effect of Genotype Group (F=.04, df=2,25, p.96, η^2=.003), no main effect of Type of Interference (F=2.02, df=2,25, p=.17, η^2=.075), and no Genotype X Type of Interference interaction (F=1.19, df=2,25, p=.32, η^2=.075). The main effect of Type of Interference interaction (F=12.18, df=1,35, p=.001, η^2=.258) was followed up with a t-test (t=-3.18, df=37, p=.003) that showed the spatial condition (M=16.60, SD=7.21) produced greater accuracy impairment than the verbal condition (M=13.53, SD=4.5).

Although the initial Two Way Repeated Measures ANOVA did not reveal a Genotype Group effect (F=1.29, df=2,60, p=.28, η^2=.04), it did show the earlier-seen main effect for Diagnostic Group (F=5.65, df=1,60, p=.02) where the schizophrenia patients were less accurate than bipolar disorder patients. When it showed the earlier-seen main effect for Type of Interference (Greenhouse-Geisser, F=11.91, df=1,60, p=.001, η^2=.166), a follow up t-test (t=3.61, df=65, p=.001) indicated that spatial interference impaired accuracy more than the verbal interference. There was no Diagnostic Group X Type of Interference interaction (Greenhouse-Geisser, F=2.72, df=1,60, p=.10, η^2=.043) nor Genotype Group X Type of Interference interaction (Greenhouse-Geisser, F=.13, df=2,60, p=.88, η^2=.004).

To summarize, for the Delayed Response Task, the genotype groups did not differ when examined within each patient group. The main effects of Diagnostic Group (i.e. bipolar disorder patients were more accurate than schizophrenia patients on a spatial task of maintenance working memory) and Type of Interference (i.e. spatial interference

creates greater impairment to accuracy than verbal interference) reflect results reported earlier.

A Two Way ANOVA for Self Ordered Pointing indicated that there was no Genotype Group effect (F=.99, df=2,73, p=.37, η^2=.027) nor Diagnostic Group X Genotype Group interaction (F=2.34, df=2,72, p=.10, η^2=.060). Figure 9 shows the main effect for Diagnostic Group (F=12.64, df=1,73, p=.001) where the schizophrenia patients (M=25.66, SD=10.90, n=50) required more trials to solve the task than bipolar disorder patients (M=18.76, SD=6.95, n=29). Although the patient-only sample examined earlier did not find diagnostic group differences, the finding of such diagnostic group differences in this analysis could be due to the fact that the samples of these two analyses vary in the following ways: 1) the age range of this sample (i.e. older than 22 years and younger than 68) differs slightly from the patient-only sample examined earlier (i.e. older than 23 years and younger than 68), 2) this sample does not include the nonpsychiatric controls and, 3) this sample only includes those patients with genotyping data.

A Two Way ANOVA performed on the Digit Span Backwards showed the earlier-reported main effect for Diagnostic Group (F=19.70, df=1,82, p<.0005, η^2=.194) where the bipolar disorder patients recalled more reversed items than the schizophrenia patients. Although the Two Way ANOVA for Digit Span Backwards did not show a Genotype Group effect (F=.70, df=2,82, p=.50, η^2=.017), Figure 10 shows there was a Diagnostic Group X Genotype Group interaction (F=5.35, df=2,82, p=.007, η^2=.115). Follow up One Way ANOVAs comparing Genotype Groups were performed separately

for first schizophrenia patients and then bipolar disorder patients.[5] For schizophrenia patients, a trend (F=2.64, df=2,55, p=.08, η^2=.088) indicated that the Heterozygote group (M=4.80, SD=.91, n=25) recalled more items than the Val/Val group (M=4.10, SD=.85, n=20, p=.03). The Met/Met group (M=4.54, SD=1.4, n=13) did not differ from either the Val/Val (p=.23) or Heterozygote (p=.46) groups. For bipolar disorder patients, there was no main effect for Genotype Groups (F=2.43, df=2,27, p=.11, η^2=.152). For the Digit Span Backward, schizophrenia patients with a Heterozygote genotype demonstrated better low-demand manipulation working memory than Val homozygotes. The main effect of diagnostic group (i.e. schizophrenia patients could not reverse and recall as many digits as bipolar disorder patients) reflected the results found earlier.

A Two Way ANOVA conducted on Letter Number Sequencing revealed the earlier-reported main effect for Diagnostic Group (F=13.78, df=1,78, p<.0005, η^2=.150) where the bipolar disorder patients recalled and sequenced more items than the schizophrenia patients. Although the Two Way ANOVA for Letter Number Sequencing did not show a Genotype Group effect (F=.09, df=2,78, p=.92, η^2=.002), Figure 11 shows

[5] To further examine the Diagnostic Group X Genotype Group interaction, follow up One Way ANOVAs comparing patient groups were separately performed within each Genotype Group. For Val homozygotes, a main effect for Diagnostic Group (F=23.44, df=1,26, p<.0005) indicated that the schizophrenia patients ((M=4.10, SD=.85, n=20) recalled less reversed items than the bipolar disorder patients (M=6.25, SD=1.5, n=8). For Met homozygotes, a main effect for Diagnostic Group (F=4.86, df=1,21, p=.04) showed that the bipolar disorder patients (M=5.80, SD=1.3, n=10) outperformed the schizophrenia patients (M=4.54, SD=1.4, n=13). For Heterozygotes, there was no main effect of Diagnostic Group (F=.09, df=1,35, p=.76). The Diagnostic Group X Genotype Group interaction for Val homozygotes is similar to the Delayed Response Task results where the schizophrenia patients were impaired compared to the bipolar disorder patients. The interaction for Met homozygotes similarly revealed schizophrenia patients were impaired compared to bipolar disorder patients.

there was a Diagnostic Group X Genotype Group interaction (F=5.49, df=2,78, p=.006, η^2=.123). Follow up One Way ANOVAs comparing Genotype Groups were performed separately for first schizophrenia patients and then bipolar disorder patients.[6] For the schizophrenia patients, a main effect (F=3.43, df=2,51, p=.04, η^2=.119) indicated that the Heterozygote group (M=5.04, SD=.75, n=24) sequenced and recalled more items than the Met/Met group (M=4.25, SD=.75, n=12, p=.02) and trended to sequence and recall less items than the Val/Val group (M=4.56, SD=1.15, n=18, p=.09). The Val and Met homozygotes did not differ from each other (p=.37). For bipolar disorder patients, no main effect for Genotype Groups were found (F=2.14, df=2,27, p=.14, η^2=.137). For the Letter Number Sequencing Task, schizophrenia patients with a Heterozygote genotype demonstrated better high-demand manipulation working memory than those with a Met homozygote genotype. The main effect of Diagnostic Group (i.e. schizophrenia patients

[6] To further examine the Diagnostic Group X Genotype Group interaction, follow up One Way ANOVAs comparing patient groups were separately performed within each Genotype Group. For Val homozygotes, a main effect of Diagnostic Group (F=5.37, df=1,24, p=.03) indicated that the schizophrenia patients (M=4.56, SD=1.1, n=18) recalled less items than the bipolar disorder patients (M=5.63, SD=.92, n=8). For Met homozygotes, a main effect (F=16.54, df=1,20, p=.001) indicated that the bipolar disorder patients (M=5.80, SD=1.0, n=10) outperformed the schizophrenia patients (M=4.25, SD=.75, n=12). For Heterozygotes, there was no main effect of Diagnostic Group (F=.15, df=1,34, p=.70). The Diagnostic Group x Genotype Group interaction for this high-demand manipulation task mirrored the results for Delayed Response Task and Digit Span Backward where once again, among Val homozygotes, the bipolar patients performed better than schizophrenia patients. That is, for the Letter Number Sequencing task, the bipolar disorder patients were able to sequence and recall more items than the schizophrenia patients. For Met homozygotes, the Letter Number Sequencing results showed this same patient group difference; a difference that was earlier found for Met homozygotes on the Digit Span Backward.

could not sequence and recall as many items as bipolar disorder patients) reflected results found earlier.

Comparison of Genotype Groups and Relative Groups on Individual Tasks (Includes Relative Groups Only)

Working Memory Performance

To further understand if variation in the genotypes would be associated with variation in working memory performance within the groups, genotype groups and diagnostic groups among the patients' relative groups were examined next. These samples included participants older than 22 years and younger than 68 years. A Chi Square indicated that there was no difference between genotype groups in their proportions of ethnic groups $X^2(4, n=100)=6.53$, $p=.16$. For relatives of schizophrenia patients as well as relatives of bipolar disorder patients, the respective percentages of ethnicity for each group were as follows: Anglo Saxon 94.4% and 93.1%, Eastern European 0% and 3.4%, Russian 0% and 3.4%, Mexican Hispanic 1.4% and 0%, and African American 4.2% and 0%.

A Two Way Repeated Measures ANOVA for the Delayed Response Task was conducted using Diagnostic Group (Relatives of Schizophrenia Patients and Relatives of Bipolar Disorder Patients) and Genotype Group (Val/Val, Heterozygotes, and Met/Met) as between-subjects factors and Type of Interference (Spatial and Verbal) as the within-subjects factor. The ANOVA revealed no main effect of Diagnostic Group ($F=.36$, $df=1,85$, $p=.55$, $\eta^2=.004$) or Genotype Group ($F=.95$, $df=2,85$, $p=.39$, $\eta^2=.022$) and no Diagnostic Group X Genotype Group interaction ($F=.03$, $df=2,85$, $p=.97$, $\eta^2=.001$).

When the earlier-reported main effect for Type of Interference (Greenhouse-Geisser F=9.60, df=1,85, p=.003, η^2=.101) was found, the follow up t-test (t=-4.93, df=90, p<.0005) indicated that spatial interference (M=14.47, SD=4.54, n=91) created greater impairment than the verbal interference (M=12.61, SD=3.59, n=91). There was a trend for a Diagnostic Group X Type of Interference interaction (Greenhouse-Geisser F=3.27, df=1,85, p=.06, η^2=.042). Figure 12 shows there was also a Genotype Group X Type of Interference interaction (Greenhouse-Geisser F=4.80, df=2,85, p=.01, η^2=.102)[7]. Once again for the Spatial Delayed Response Task, the use of spatial stimuli (M=14.47, SD=4.54, n=91) as the delay period interference produced greater deficits in maintenance ability than verbal stimuli (M=12.61, SD=3.58, n=91). There was no Diagnostic Group X Genotype Group X Type of Interference interaction (Greenhouse-Geisser F=1.15, df=2,85, p=.32, η^2=.026). For the Spatial Delayed Response Task, there was no difference between the genotype groups within the relatives of schizophrenia patients and relatives of bipolar disorder patients.

A Two Way ANOVA on the Self Ordered Pointing task indicated that there was no main effect for Diagnostic Group (F=.66, df=1,81, p=.42, η^2=.008), no main effect for Genotype Group (F=.26, df=2,81, p=.77, η^2=.006), nor Diagnostic Group X Genotype Group interaction (F=1.86, df=2,81, p=.16, η^2=.044).

[7] A follow up One Way ANOVA comparing the spatial interference performance of the genotype groups (F=2.7, df=2, 88, p=.07) confirmed that the Heterozygote maintenance ability (M=15.37, SD=4.35, n=45) was impaired compared to Met homozygotes (M=12.83, SD=3.89, n=26, p=.02) but not Val homozygotes (M=14.59, SD=5.30, n=20, p=.19). Heterozygotes and Val homozygotes did not differ from each other (p=.51). A follow up One Way ANOVA comparing the verbal interference performance of the genotype groups showed no main effect of Genotype Groups (F=.009, df=2,88, p=.99).

A Two Way ANOVA on the Digit Span Backwards indicated that although there was no main effect for Diagnostic Group (F=.28, df=1,91, p=.59, η^2=.003) or Genotype Group (F=.79, df=2,91, p=.45, η^2=.017), there was Diagnostic Group X Genotype Group interaction (F=3.54, df=2,91, p=.03, η^2=.072). Follow up One Way Univariate ANOVAs compared Genotype Groups, first for relatives of schizophrenia patients and then for relatives of bipolar disorder patients.[8] No main effects of Genotype Group were found for either relatives of schizophrenia patients (F=.97, df=2,67, p=.38, η^2=.028) or relatives of bipolar disorder patients (F=2.46, df=2,24, p=.11, η^2=.170). For the Digit Span Backwards, there was no difference between the genotype groups within the relatives of schizophrenia patients and relatives of bipolar disorder patients.

A Two Way ANOVA on the Letter Number Sequencing task indicated that there was no main effect for Diagnostic Group (F=.29, df=1, 90, p=.59, η^2=.003) and no Diagnostic Group X Genotype Group interaction (F=.59, df=2, 90, p=.55, η^2=.013). Although there was a trend for a main effect for Genotype Group (F=2.56, df=2, 90, p=.08, η^2=.054), a follow up One Way ANOVA did not reveal any significant differences between the Genotype Groups (F=1.99, df=2,93, p=.14, η^2=.041). For the Letter Number

[8] The Diagnostic Group X Genotype Group interaction was further examined by conducting One Way Univariate ANOVAs comparing relatives groups within each separate genotype group. Figure 13 shows a follow up One Way ANOVA (F=6.77, df=1,47, p=.01) conducted only for Heterozygotes showed that the relatives of bipolar disorder patients (M=5.38, SD=1.0, n=13) reversed and recalled more digits than the relatives of schizophrenia patients (M=4.61, SD=.87, n=26). For Met homozygotes (F=1.00, df=1,23, p=.33) as well as Val homozygotes (F=2.07, df=1,21, p=.16), there were no main effects.

Sequencing task, there was no difference between the genotype groups within the relatives of schizophrenia patients and relatives of bipolar disorder patients.

For these analyses, it was of specific interest to see if there would be variation among genotype groups when examined within each relative group. Surprisingly, there appeared to be no differences between genotype groups within the separate groups of relatives of schizophrenia patients as well as bipolar disorder patients.

Comparison of Groups Across Tasks (Includes All Groups)

Demographics

Of additional interest was whether the diagnostic groups would differ across working memory subprocesses, as indexed by the tasks included in the present experiment. Table 6 summarizes the demographic characteristics of each Diagnostic Group examined across tasks. When participants were restricted to only those older than 22 years and younger than 68, an One Way Univariate ANOVA revealed that the groups did not differ in their ages (F=1.82, df=4,190, p=.126). A Chi Square test revealed a significant difference between the observed and expected numbers of males and females for the diagnostic groups, $X^2(4, n=195) = 16.01$, p=.003). Consequently, Gender was made a between subjects variable along with Diagnostic Group in the Repeated Measures ANOVA examining working memory performance across all tasks.

An One Way Univariate ANOVA on IQ score (F=5.70, df=4,189, p<.0005) indicated that the schizophrenia patients had a lower IQ than the nonpsychiatric controls (p=.001), bipolar disorder patients (p<.0005), relatives of schizophrenia patients (p=.001), and relatives of bipolar disorder patients (p=.001). In addition, the relatives of

schizophrenia patients had lower IQ than the bipolar disorder patients (p=.08). Pearson Product Moment Correlations collapsed across all participant groups indicated that the z-scores for working memory performance on the Digit Span Backwards (r=.44, df=189, p<.0005), Letter Number Sequencing (r=.46, df=187, p<.0005), Self Ordered Pointing (r=.25, df=191, p=.001), verbal interference condition of the Spatial Delayed Response Task (r=.31, df=191, p<.0005), and spatial interference condition of the Spatial Delayed Response Task (r=.29, df=191, p<.0005) were significantly correlated with IQ. As expected, the sensorimotor condition of the Spatial Delayed Response Task was not correlated with IQ (r=.04, df=191, p=.55). ANCOVAs with IQ as a covariate were conducted to compare group performance on working memory tasks.

An One Way Univariate ANOVA (F=2.41, df=4,189, p=.05) revealed that the schizophrenia patients had less years of education than nonpsychiatric controls (p=.004), bipolar disorder patients (p=.06), and relatives of schizophrenia patients (p=.09). In addition, the relatives of the bipolar disorder patients had less education than the nonpsychiatric controls (p=.07). For reasons stated earlier, ANCOVAs were not performed using Education as a covariate.

Working Memory Performance

To examine performance across the various types of working memory tasks, a Two Way Repeated Measures ANOVA was performed where Diagnostic Group (Nonpsychiatric Controls, Schizophrenia Patients, Bipolar Disorder Patients, Relatives of Schizophrenia Patients, and Relatives of Bipolar Disorder Patients) and Gender (Male and Female) were between-subjects factors while Task (DRT Verbal, DRT Spatial, Self

Ordered Pointing, Digit Span Backwards, and Letter Number Sequencing) was the within-subjects factor. There as no main effect for Gender (F=.07, df=1,177, p=.78, η^2=.000), no Gender X Diagnostic Group interaction (F=.09, df=4,177, p=.98, η^2=.002), no Task x Gender interaction (F=1.38, df=4,708, p=.24, η^2=.008), no Task X Diagnostic Group interaction (F=.88, df=16,708, p=.57, η^2=.020), or Task X Gender X Diagnostic Group interaction (F=.79, df=16,708, p=.69, η^2=.018). When examined with an ANCOVA with IQ as covariate, the results for Gender (F=.13, df=1,176, p=.72, η^2=.001), Gender X Diagnostic Group (F=.23, df=4,176, p=.92, η^2=.005), Task X Diagnostic Group (Greenhouse-Geisser F=.83, df=16,704, p=.65, η^2=.02), Task X Gender (Greenhouse-Geisser F=1.39, df=4,704, p=.23, η^2=.008), and Task X Gender X Diagnostic Group (Greenhouse-Geisser F=.76, df=16,704, p=.71, η^2=.017) were changed little.

There was a main effect of Diagnostic Group (F=3.96, df=4,177, p=.004, η^2=.082). When examined with an ANCOVA with IQ as covariate, the main effect for Diagnostic Group remained (F=2.32, df=4,176, p=.059, η^2=.050). A follow up One Way ANOVA comparing Diagnostic Groups on the average of all tasks' z-scores, confirmed the main effect (F=4.39, df=4,190, p=.002, η^2=.085) and indicated that the performance of schizophrenia patients (M=.55, SD=.61, n=36) was impaired compared to nonpsychiatric controls (M=-.01, SD=.63, n=44, p<.0005), bipolar disorder patients (M=-.14, SD=.76, n=29, p=.002), relatives of bipolar disorder patients (M=-.13, SD=.47, n=25 p=.009), relatives of schizophrenia patients (M=-.30, SD=.56, n=61, p=.057) while the

relatives of schizophrenia patients demonstrated impaired performance compared to nonpsychiatric controls (p=.02). See Figure 14.

There was also a main effect of Task (F=.7.17, df=4,708, p<.0005, η^2=.039). When examined with an ANCOVA with IQ as covariate, the main effect of Task remained (F=4.66, df=4,704, p=.001, η^2=.026). Follow up t-tests indicated that the Self Ordered Pointing task (M=.07, SD=.86, n=193) did not produce as much impairment as the verbal interference condition of the Spatial Delayed Response Task (t=-4.26, df=192, p<.0005, M=-.29, SD=.95, n=193), spatial condition of the Spatial Delayed Response Task (t=-4.05, df=192, p<.0005, M=-.27, SD=1.01, n=193), Digit Span Backward task (t=4.61, df=189, p<.0005, M=-.31, SD=.84, n=190), and Letter Number Sequencing task (t=4.93, df=188, p<.0005, M=-.40, SD=1.09, n=189). See Figure 14. Follow up t-tests indicated that the verbal interference condition of the Spatial Delayed Response Task did not differ from the spatial condition of the Spatial Delayed Response Task (t=-.30, df=193, p=.76), Digit Span Backward (t=-.14, df=189, p=.89), or Letter Number Sequencing (t=-.39, df=189, p=1.09). The spatial condition of the Spatial Delayed Response Task did not differ from Digit Span Backward (t=.43, df=189, p=.67) or Letter Number Sequencing (t=1.36, df=188, p=.17). Also, the Digit Span Backward did not differ from the Letter Number Sequencing (t=1.27, df=188, p=.20).

To summarize, when diagnostic groups were compared on working memory performance collapsed across tasks, it was found that schizophrenia patients were more impaired than nonpsychiatric controls, bipolar disorder patients, relatives of bipolar disorder patients, and relatives of schizophrenia patients. Additionally, relatives of

schizophrenia patients were more impaired than nonpsychiatric controls. When examining for differences between the various working memory tasks, only the Self Ordered Pointing task differed from the rest of the tasks in that it did not appear to reveal any deficits. Specifically, this task of the monitoring subprocess of working memory did not appear to reveal deficits compared to the tasks that reflected the maintenance and manipulation subprocesses of working memory.

Since previous research by Conklin, Curtis, and Iacono (2000) found a monitoring deficit in schizophrenia patients and their relatives compared to nonpsychiatric controls, the finding that most groups required less trials to complete the Self Ordered Pointing task than the nonpsychiatric controls was surprising. As far as it is known, no inadvertent but systematic aberration occurred in the administration of the SOP task and influenced the groups' performance. Despite this, Figure 14 shows that the schizophrenia patients constituted the only group that did not outperform the nonpsychiatric controls, although their performance difference from nonpsychiatric controls was not significant. The other notable, pattern visible in Figure 14 is the gradient of performance for the various groups which shows: 1) the relative groups performed similar to each of their respective patient groups and, 2) the bipolar disorder spectrum groups did worse than the nonpsychiatric controls but better than the schizophrenia spectrum groups.

DISCUSSION

The first question examined in the present study was whether deficits in the working memory subprocesses of maintenance, monitoring, and manipulation were specific to schizophrenia patients or also present in bipolar disorder patients. Schizophrenia patients were found to have impaired ability for maintenance as measured by a visuomotor version of the Spatial Delayed Response Task. Compared to both nonpsychiatric controls and bipolar disorder patients, they also demonstrated deficits in low and high demand manipulation as measured by the Digit Span Backwards and Letter Number Sequencing tasks, respectively. These results are in line with previous research that has reported deficits in schizophrenia patients compared to nonpsychiatric controls in maintenance using the Spatial Delayed Response Task (Glahn et al., 2006; Kim et al., 2004; Leiderman et al., 2004), low demand manipulation as measured by the Digit Span Backwards (Alptekin et al., 2005; Bozikas et al., 2006; Conklin et al., 2005; & Glahn et al., 2006), and high demand manipulation as measured by the Letter Number Sequencing task (Conklin et al., 2005; Gold et al., 1997; Goldberg et al., 1998; Pukrop et al., 2003). Only two previous studies have directly compared schizophrenia and bipolar disorder patients on working memory subprocesses. The present results replicate a study by Gooding & Tallent (2001), which found a maintenance impairment (as measured by the Spatial Delayed Response Task) in schizophrenia patients compared to nonpsychiatric controls and bipolar disorder patients. For low demand manipulation using the Digit Span Backwards, the present results replicated the finding by Gourovitch et al. (1999) who did not find a Digit Span Backwards deficit in monozygotic twins discordant for

bipolar disorder compared to nonpsychiatric controls. However, Gourovitch and colleagues did find a deficit in affected co-twins for the Brown Peterson Task (a maintenance task of verbal working memory with distraction delay, see description earlier). A focus of the Gourovitch study was to compare the cognitive performance of the bipolar disorder patients to an earlier-studied group of schizophrenia patients. Although Gourovitch and colleagues did not report the results of the comparison for individual tasks, they did report that the deficits found in the bipolar disorder patients were much more mild than those seen in the schizophrenia patients. Unlike studies by Thompson and colleagues (2001a; 2005) that reported low demand manipulation impairment (as measured by the Digit Span Backwards) in bipolar disorder patients compared to nonpsychiatric controls, the present study did not find low demand manipulation deficits in bipolar disorder patients. The first of the studies by Thompson and colleagues (2001a) was reported in the form of a poster abstract and therefore experimental details reported are few. The second of the Thompson studies (2005) used 54 bipolar disorder Type I patients, 9 bipolar disorder Type II patients, and 5 rapid cycling patients; half of all patients had previously received ECT. In contrast, the present study excluded patients with a history of ECT treatment as it is possible that excitotoxic seizures produced by the procedure may create brain damage that results in cognitive deficits. It is possible that the bipolar disorder patients of both studies by Thompson and colleagues were impaired by the effects of ECT treatments.

In the present study, schizophrenia patients also demonstrated deficits in monitoring compared to bipolar disorder patients but only for samples of those over 22

and under 68 years of age and for whom genotyping data was available. Earlier studies (Chey et al., 2002; Conklin et al., 2005) have reported a monitoring deficit (as measured by the Self Ordered Pointing task) in schizophrenia patients compared to nonpsychiatric controls. In addition, although earlier studies reported a monitoring deficit in bipolar disorder patients compared to nonpsychiatric controls (Thompson et al., 2001a; 2005), the present study did not find a performance difference between these groups. As stated earlier, these early studies by Thomson did differ from the present experiment by using patients with a history of ECT. The present experiment's gamut of results regarding the Self Ordered Pointing task has been generally peculiar and it is uncertain what factors may account for this.

In the present study, diagnostic groups were also compared on working memory performance collapsed across all tasks of working memory subprocesses. The performance of schizophrenia patients was worse than the nonpsychiatric controls, bipolar disorder patients, relatives of bipolar disorder patients, as well as relatives of schizophrenia patients. As working memory has been identified as an executive function of the PFC, the present findings provide support for the suggestion that schizophrenia is associated with an abnormally functioning PFC and likely has pathophysiology related to that brain area. The lack of impairment in bipolar disorder patients on any of the working memory subprocess tasks suggests that the PFC is not greatly affected in this patient population. These results add strength to the body of research evidence that indicates schizophrenia and bipolar disorder are distinct illnesses with differing pathophysiologies.

The second question examined in the present study was whether the relatives of schizophrenia patients and relatives of bipolar disorder patients would manifest deficits in the working memory processes of maintenance, monitoring, and manipulation. Although no differences were revealed between nonpsychiatric controls and the patients' relative groups in monitoring (as measured by Self Ordered Pointing), the relatives of schizophrenia patients showed poorer performance than nonpsychiatric controls in low and high demand manipulation as measured by the Digit Span Backwards and Letter Number Sequencing tasks, respectively, and a trend for poorer performance in maintenance (using the Spatial Delayed Response Task). Although these results differ from Conklin et al. (2005) which reported a monitoring deficit in relatives of schizophrenia patients compared to nonpsychiatric controls, the present findings support previous studies that have found the relatives of schizophrenia patients impaired compared to nonpsychiatric controls with regard to maintenance using the oculomotor Spatial Delayed Response Task (McDowell et al., 2001; Park et al., 1995), low demand manipulation using the Digit Span Backwards (Conklin et al., 2005; Trandafir et al., 2006), and high demand manipulation using the Letter Number Sequencing task (Conklin et al., 2006). Only one previous study has directly compared relatives of schizophrenia patients and relatives of bipolar disorder patients on maintenance (using a high demand spatial working memory task with delay) and low demand manipulation using the Digit Span Backwards (Keri et al., 2001). Similar to the present study, they found a maintenance deficit in relatives of schizophrenia patients compared to relatives of bipolar disorder patients and nonpsychiatric controls. Whereas the present study showed the

relatives of schizophrenia patients had a low demand manipulation deficit compared to nonpsychiatric controls, Keri et al. (2001) found no difference between relatives of schizophrenia patients, nonpsychiatric controls, and relatives of bipolar disorder patients. Keri and colleagues (2001) did point out that their group of patients had a milder course of illness and that their relatives had high IQ, education, and psychosocial functioning. It is possible that their group of relatives was not representative of a genetically at-risk population. Also, although there has been a report of a low demand manipulation deficit in the relatives of bipolar disorder patients, as measured by the Digit Span Backwards (Ferrier et al., 2004), the present experiment did not find working memory deficits in the relatives of bipolar disorder patients. Unlike the relatives of bipolar disorder patients included in the present study, those of Ferrier and colleagues included individuals with previous Axis I disorders (e.g. Major Depressive Disorder, Panic Disorder, and Social Phobia).

It should be noted that when the present analyses were rerun with the variance due to same family membership accounted for, all differences remained significant. This would suggest that differences between families were not underlying the performance difference between relatives of schizophrenia patients and nonpsychiatric controls in maintenance as well as low and high demand manipulation. Considering these results, impairments in maintenance and manipulation appear to be a promising endophenotypes for schizophrenia-relevant disease genes. As mentioned earlier, diagnostic groups were also compared on working memory performance collapsed across all tasks of working memory subprocesses. The relatives of schizophrenia patients demonstrated worse

performance than nonpsychiatric controls. This finding provides further support for a working memory-related endophenotype for schizophrenia vulnerability genes.

The third question examined in the present study was whether the *COMT* Val158Met polymorphism genotypes (i.e. Val homozygotes, heterozygotes, and Met homozygotes) would differ from each other in maintenance, monitoring, and manipulation. When genotype groups were compared within a sample composed of every participant, regardless of diagnostic group, no differences were revealed for any of these working memory subprocesses. As reviewed earlier, various research studies have similarly reported a lack of genotype group differences. A previous study that investigated these genotype groups in healthy children found no differences on the monitoring task of Self Ordered Pointing (Diamond et al., 2004). Bilder et al. (2002) reported no differences in genotype gropus on the Spatial Delayed Response Task and n-back for their sample of nonpsychiatric controls. Bruder et al. (2005) similarly found no genotype group differences for the WCST in their sample of controls. A study that compared these genotype groups in healthy adults found no significant differences on the WCST or the high demand manipulation task of Letter Number Sequencing, although it was observed that the Met allele was associated with better, though nonsignificant, performance on the Letter Number Sequencing than the Heterozygote and Val homozygote genotype groups (Bruder et al., 2005). In examining schizophrenia patients and nonpsychiatric controls, Bosia et al. (2007) reported no differences between genotype groups on a digit sequencing working memory task. Ho et al. (2005) also found no differences among genotype groups for the WCST and Digit Span Backwards.

Although much of the previous research has reported a cognitive advantage associated with greater Met158 allele loading, a considerable number of studies have reported a lack of working memory differences among the genotype groups. Tunbridge et al. (2006) suggested that multiple factors could contribute to an individual's PFC dopamine status along the inverted U-curve. Hypofrontal dopamine could be a consequence of increasing age after the PFC has already reached maturity. Trait-related factors such as ADHD and Parkinson's Disease would similarly render below-optimal levels of dopamine. State-related variables such as stress or amphetamine psychosis could push an individual beyond dopamine's zone of peak PFC performance.

COMT Val158Met genotype might also interact with various factors to influence PFC function. For example, Smyrnis et al. (2007) reported no Val158Met genotype group differences on spatial working memory but findings from their structural equation modeling indicate that, cognitive performance worsened with greater presence of negative schizotypy. In addition, increases in Val allele loading had a modulating effect upon the cognition-schizotypy relationship that led the authors to suggest that, among individuals exhibiting a high degree of negative schizotypy, greater degree of cognitive impairment may result from increased presence of Val allele.

The results of Meyer-Lindenberg et al. (2006), Tan et al. (2007), and Roffman et al. (2008), and Xu et al. (2007) provided evidence that *COMT* Val158Met interacts with other genes as well as other *COMT* polymorphisms to affect working memory performance. Several of these studies have suggested that such interactions may account

for previous findings reporting discrepant results in the *COMT* Val158Met genotyping literature.

In the present study, when genotype groups were compared within separate samples for each diagnostic group, a couple of interesting results were found. Genotype groups did not differ from each other on maintenance or monitoring when compared within schizophrenia, bipolar disorder, relatives of schizophrenia patients, as well as relatives of bipolar disorder patients. The genotype groups also did not differ from each other on low or high demand manipulation within either patients' relative groups. However, for low demand manipulation, there was a trend regarding the performance for schizophrenia patients where Val homozygotes demonstrated poorer performance than heterozygotes. Also, for high demand manipulation performance of schizophrenia patients, the Met homozygotes were impaired compared to heterozygotes who trended impairment compared to Val homozygotes.

No previous studies have compared *COMT* Val158Met polymorphism genotype groups within schizophrenia for the subprocesses of maintenance, monitoring, or manipulation using the same tasks as the present study. However, previous experiments that have used the executive tasks of n-back or WCST (i.e. tasks that likely include maintenance and monitoring) have generally found that the Val homozygotes perform worse than the heterozygote and Met homozygote groups (Egan et al., 2001; Galderisi et al., 2005; Goldberg et al., 2003; Joober et al., 2002). The authors of these previous studies generally argue that the Val allele is likely associated with reduced prefrontal dopamine and poorer executive function while the Met allele would increase prefrontal

dopamine and relate to better executive functioning. The present finding in schizophrenia patients of a trend for worse low demand manipulation in Val homozygotes than in heterozygotes somewhat support the previous research. Although this finding was derived from a schizophrenia patient sample, it is also somewhat in agreement with Bilder and colleagues' (2002) results for nonpsychiatric controls which found poorer Val homozygote performance for manipulation. Bilder et al. (2002) suggested that the higher order working memory subprocess of manipulation is more directly related to the *COMT* gene than the other working memory subprocesses.

However, the present research also found among schizophrenia patients that the Met homozygotes demonstrated high demand manipulation impairment compared to the heterozygotes who trended a deficit compared to the Val homozgyotes. Considering the existing literature on genotype group performance differences in executive function, this result was surprising. An inverted U-shaped function has been purported where intermediate levels of dopamine are associated with a maximally performing PFC while low and high levels of dopamine relate to an inefficiently performing PFC (Tunbridge et al., 2006). If the intermediate Val allele loading of Val158Met polymorphism heterozygotes can be considered intermediate in its effect on prefrontal dopamine, then the present result of worse Met homozygote manipulation than heterozygotes is explainable by this U-shaped function theory. However, it does not explain the present trend for worse heterozygote manipulation than Val homozygotes and this theory would be inconsistent with the existing genotyping studies in schizophrenia.

There were several weakness of the present study. Analyses included small sample sizes for patient groups and relatives of bipolar disorder patients. Although the schizophrenia patient group demonstrated clear deficits for all working memory subprocesses, it is possible that subtle impairments in bipolar disorder patients and their relatives might have been revealed with larger samples included in the analyses. Another issue regarded the peculiar results of the monitoring task, Self Ordered Pointing. Except for the schizophrenia patients, all groups scored better on this task than the nonpsychiatric controls although the differences were not significant. As no unusual aspects of presentation, administration, or scoring are known of, it is unclear why the Self Ordered Pointing results were peculiar. Future studies on specific working memory processes may greatly benefit from continuing to explore whether subprocess impairments are associated with particular *COMT* genotypes. Also, it might be useful for future researchers to determine the transmission of alleles associated with impairment in specific types of working memory subprocesess.

REFERENCES

Abi-Dargham, A., Mawlawi, O., Lombardo, I., Gil, R., Martinez, D., Huang, Y., Hwang, D., Keilp, J., Kochan, L., Van Heertum, R., Gorman, J. M., & Laruelle, M. (2002). Prefrontal dopamine D1 receptors and working memory in sz. Journal of Neuroscience, 22(9), 3708-3718.

Adler, C. M., Holland, S. K., Schmithorst, V., Tuchfarber, M. J., & Strakowski, S. M. (2004). Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. Bipolar Disorders, 6, 540-549.

Aleman, A., Hijman, R., de Haan, E. H. F., & Kahn, R. S. (1999). Memory impairment in schizophrenia: A meta-analysis. American Journal of Psychiatry, 156(9), 1358-1366.

Appels, M. C. M., Sitskoorn, M. M., Westers, P., Lems, E., & Kahn, R. S. (2003). Cognitive dysfunctions in parents of schizophrenic patients parallel the deficits found in patients. Schizophrenia Research, 63, 285-293.

Alptekin, K., Akvardar, Y., Akdede, B. B. K., Dumlu, K., Isik, D., Pirincci, G., Yahssin, S., & Kitis, A. (2005). Is quality of life associated with cognitive impairment in schizophrenia? Progress in Neuro-Psychopharmacology and Biological Psychiatry, 29, 239-244.

Andreasen, N. C., O'Leary, D. S., Flaum, M., Nopoulos, P., Watkins, G. L., Boles Ponto, L. L., & Hichwa, R. D. (1997). Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naïve patients. Lancet, 349, 1730-1734.

Arduini, L., Kalyvoka, A., Stratta, P., Rinaldi, O., Danueluzzo, E., & Rossi, A. (2003). Insight and neuropsychological function in patients with schizophrenia and bipolar disorder with psychotic features. Canadian Journal of Psychiatry, 48(5), 339-341.

Arias, B., Serretti, A., Lorenzi, C., Gasto, C., Catalan, R., & Fananas, L. (2006). Analysis of COMT gene (val 158 met polymorphism) in the clinical response to SSRIs in depressive patients of European origin. Journal of Affective Disorders, 90, 251-256.

Asarnow, R. F., & MacCrimmon, D. J. (1981). Span of apprehension deficits during the postpsychotic stages of schizophrenia: A replication and extension. Archives of General Psychiatry, 38, 1006-1011.

Avrampoulous, D., Stefanis, N. C., Hantoumi, I., Smyrnis, N., Evdokimidis, I., & Stefanis, C. N. (2002). Molecular Psychiatry, 7, 706-711.

Axelrod, B. N., Goldman, R. S., Tompkins, L. M., & Jiron, C. C. (1994). Poor differential performance on the Wisconsin Card Sorting Test in schizophrenia, mood disorder, and traumatic brain injury. Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 1, 20-24.

Baddeley, A. D. (1996). Exploring the central executive. Quarterly Journal of Experimental Psychology: Human Experimental Psychology, 49, 5-28.

Baddeley, A. D. (2000). The episodic buffer: a new component of working memory? Trends in Cognitive Science, 4, 417-423.

Baddeley, A. D., & Della Sala, S. (1998). Working memory and executive control. In A. C. Roberts (Ed.), The prefrontal cortex: Executive and cognitive functions (pp. 9-21). New York, NY, US: Oxford University Press.

Baddeley, A.D., & Hitch, G. (1974). Working memory. In G.H. Bower (Ed.), The psychology of learning and motivation: Advances in research and theory (Vol. 8, pp. 47--89). New York: Academic Press.

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

Badner & Gershon (2004). Meta-analysis of whole-genome linkage scans of bipolar disorder and sz. Molecular Psychiatry, 7, 405-411.

Barch, D. M., Sheline, Y. I., Csernansky, J. G., & Snyder, A. Z. (2003). Working memory and prefrontal cortex dysfunction; Specificity to schizophrenia compared with major depression. Biological Psychiatry, 53, 376-384.

Barnett, J. H., Heron, J., Ring, S. M., Golding, J., Goldman, D., Xu, K., & Jones, P. B. (2007). Gender-specific effects of the catechol-O-methyltransferase *val*108/158*met* polymorphism on cognitive function in children. American Journal of Psychiatry, 164(1), 142-149.

Bearden, C.E., Hoffman, M, & Cannon, T.D. (2001). The neuropsychology and neuroanatomy of bipolar affective disorder: a critical review. Bipolar Disorders, 3, 106-150.

Berretini, W. (2003). Evidence for shared susceptibility in bipolar disorder and schizophrenia. American Journal of Medical Genetics, Part C., 123C, 59-64.

Berrettini, W. (2004). Bipolar disorder and schizophrenia: convergent molecular data. Neuromolecular Medicine, 5, 109-117.

Bertolino, A. Callicott, J. H., Elman, I., Mattay, V. S., Tedeschi, G., Frank, J. A., Breier, A., & Weinberger, D. A. (1998a). Regionally specific neuronal pathology in untreated patients with schizophrenia: A proton magnetic resonance imaging study. Biological Psychiatry, 43, 641-648.

Bertolino, A., Kumra, S., Callicott, J. H., Mattay, V. S., Lestz, R. M., Jacobsen, L., Barnett, I. S., Duyn, J .H., Frank, J. A., Rapoport, J. A., & Weinberger, D. R. (1998b). Common pattern of cortical pathology in childhood-onset and adult-onset schizophrenia as identified by proton magnetic resonance spectroscopic imaging. American Journal of Psychiatry, 155, 1376-1383.

Bertolino, A., & Weinberger, D. R. (1999). Proton magnetic resonance spectroscopy in schizophrenia. European Journal of Radiology, 30, 132-141.

Bilder, R. M., Volavka, J., Lachman, H. M., & Grace, A. A. (2004). The catechol-O-methyltransferase polymorphism: Relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacology, 29, 1943-1961.

Bilder, R. M., Volavka, J., Czobor, P., Malhotra, A. K., Kennedy, J. L., Ni, X., Goldman, R. S., Hoptman, M. J., Sheitman, B., Lindenmayer, J. –P., Citrome, L., McEnvoy, J. P., Kunz, M., Chakos, M., Cooper, T. B., & Lieberman, J. A. (2002). Neurocognitive correlates of the COMT Val158Met polymorphism in chronic schizophrenia. Biological Psychiatry, 52, 701-707.

Bosia, M., Bechi, M., Marino, E., Anselmetti, S., Poletti, S., Cocchi, F., Smeraldi, E., & Cavallaro, R. (2007). Influence of catechol-O-methyltransferase Val158Met

polymorphism on neuropsychological and functional outcomes of classical rehabilitation and cognitive remediation in schizophrenia. Neuroscience Letters, 417, 271-274.

Bozikas, V. P., Kosmidis, M. H., Kiosseoglou, G., & Karavatos, A. (2006). Neuropsychological profile of cognitively impaired patients with schizophrenia. Comprehensive Psychology, 47, 36-143.

Brebion, G., Amador, X., Smith, M. J., & Gorman, J. (1998). Memory impairment and schizophrenia: The role of processing speed. Schizophrenia Research, 30, 31-39.

Bruder, G. E., Keilp, J. G., Xu, H., Shikhman, M., Schori, E., Gorrman, J. M., & Gilliam, T. C. (2005). Catechol-o-methyltransferase (COMT) genotypes and working memory: Associations with differeing cognitive operations. Biological Psychiatry, 58, 901-907.

Buchsbaum, M. S., Haier, R. J., Potkin, S. G., Nuechterlein, K., Bracha, H. S., Katz, M., Lohr, J., Wu, J., Lottenberg, S., Jerabek, P. A., Trenary, M., Tafalla, R., Reynolds, C., & Bunney Jr., W. E. (1992). Frontostriatal disorder of cerebral metabolism in never-medicated schizophrenics. Archives of General Psychiatry, 49, 935-942.

Callicott, J.H., Bertolino, A., Mattay, V. S., Langheim, J. P., Duyn, J., Coppola, R., Goldberg, T. E., & Weinberger, D. R. (2000). Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. Cerebral Cortex, 10(11), 1078-1092.

Callicott, J. H., Egan, M. F., Mattay, V. S., Bertolino, A., Bone, A. D., Verchinski, B., & Weinberger, D. R. (2003). Abnormal fMRI response of the

dorsolateral prefrontal cortext in cognitively intact siblings of patients with schizophrenia. American Journal of Psychiatry, 160, 709-719.

Callicott, J. H., & Weinberger, D. R. (1999). Neuropsychiatric dynamics: The study of mental illness using functional magnetic resonance imaging. European Journal of Radiology, 30, 95-104.

Cannon, T. D. (2005). The inheritance of intermediate phenotypes for schizophrenia. Current Opinion in Psychiatry, 18, 135-140.

Cannon, T.D., Gasperoni, T. L., van Erp, T. G. M., & Rosso, I. M. (2001). Quantitative neural indicators of liability to schizophrenia: Implications for molecular genetic studies. American Journal of Medical Genetics, 105, 16-19.

Cannon, T. D., Glahn, D. C., Kim, J., Van Erp, T. G. M., Karlsgodt, T., Cohen, M. S., Nuechterlein, K. H., Bava, S., & Shirinyan, D. (2005). Dorsolateral prefrontal cortex activity during maintenance and manipulation of information in working memory in patients with schizophrenia. Archives of General Psychiatry, 62, 1071-1080.

Cannon, T. D., Huttunen, M. O., Lonnqvist, J., Tuulio-Henriksson, A., Pirkola, T., Glahn, D., Finkelstein, J., Hietanen, M., Kaprio, J., & Koskenvuo, M. (2000). The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. American Journal of Human Genetics, 67, 369.

Cannon, T. D., Kaprio, J., Lonnqvist, J., Huttunen, M., & Koskenvuo, M. (1998). The genetic epidemiology of schizophrenia in a Finnish twin cohort: a population-based modeling study. Archives of General Psychiatry, 55, 67-74.

Cardno, A. G., & Gottesman, I. I. (2000) Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. American Journal of Medical Genetics, 97, 12–17.

Carter, C. S., Mintun, M., Nichols, T., & Cohen, J. D. (1997). Anterior cingulated gyrus dysfunction and selective attention deficits in schizophrenia: [150] H2) PET study during single-trial Stroop task performance. American Journal of Psychiatry, 54, 1670-1675.

Carter, C. S., Perlstein, W., Ganguli, R., Brar, J., Mintun, M., & Cohen, J. D. (1998). Functional hypofrontality and working memory dysfunction in schizophrenia. American Journal of Psychiatry, 155, 1285-1287.

Cavanagh, J. T. O., van Beck, M., Muir, W., & Blackwood, D. H. R. (2002). Case-control study of neurocognitive function in euthymic patients with bipolar disorder: an association with mania. British Journal of Psychiatry, 180, 320-326.

Chan, M. W. C., Yip, J. T. H., & Lee, T. M. C. (2004). Differential impairment on measures of attention in patients with paranoid and nonparanoid schizophrenia. Journal of Psychiatric Research, 38, 145-152.

Chen, Y. L. R., Chen, Y. H. E., & Lieh-Mak, F. (2000). Semantic verbal fluency deficit as a familial trait marker in schizophrenia. Psychiatry Research, 95, 133-148.

Chen, X., Wang, X., O'Neil, A. F., Walsh, D., & Kendler, K. S. (2004). Variants in the catechol-O-methyltransferase (COMT) gene are associated with schizophrenia in Irish high-density families. Molecular Psychiatry, 9, 962-967.

Chey, J., Lee, J., Kim, Y. –S., Kwon, S. –M., Shin, Y. –M. (2002). Spatial working memory span, delayed response and executive function in schizophrenia. Psychiatry Research, 110, 259-271.

Chen, C. –H., Lee, Y. –R., Wei, F. –C., Koong, F. –J., Hwu, H. –G., & Hsiao, K. –J. (1997). Association study of N1aIII and MspI genetic polymorphisms of catechol-O-methyltransferase gene and susceptibility to schizophrenia. Biological Psychiatry, 41, 985-987.

Clark, L., Iversen, S. D., & Goodwin, G. M. (2001). A neuropsychological investigation of prefrontal cortex involvement in acute mania. American Journal of Psychiatry, 158, 1605-1611.

Coffman, J .A., Borenstein, R. A., Olson, S. C., Schwartzkopf, S. B., & Nasrallah, H. A. (1990). Cognitive impairment and cerebral structure by MRI in bipolar disorders. Biological Psychiatry, 27(11), 1188-1196.

Conkin, H. M., Curtis, C. E., Katsanis, J., & Iacono, W. G. (2000). Verbal working memory impairment in schizophrenia patients and their first-degree relatives: Evidence from the digit span task. American Journal of Psychiatry, 157(2), 275-277.

Conklin, H. M., Curtis, C. E., Calkins, M. E., & Iacono, W. G. (2005). Working memory functioning in schizophrenia patients and their first-degree relatives: cognitive functioning shedding light on etiology. Neuropsychologia, 43, 930-942.

Courtney, S. M., Ungerleider, L. G., Keil, K., Haxby, J. V. (1998). A neural system for human visual working memory. Proceedings of the National Academy of Sciences, 95, 883-890.

Daniels, J. K., Williams, N. M., Williams, J., Jones, L. A., Cardno, A. G., Murphy, K. C., Spurlock, G., Riley, B., Scambler, P., Asherson, P., McGuffin, P., & Owen, M. J. (1996). American Journal of Psychiatry, 153, 268-270.

Davidson, L. L., & Heinrichs, W. R. (2003). Quantification of frontal lobe and temporal lobe brain-imaging findings in schizophrenia: a meta-analysis. Psychiatry Research, 122, 69-87.

De Chaldee, M., Corbex, M., Campion, D., Jay, M., Samolyk, D., Petit, M., Thibaut, F., Laurent, C., & Mallet, J. (2001). No evidence for linkage between COMT and schizophrenia in a French population. Psychiatry Research, 102, 87-90.

De Chaldee, M., Laurent, C., Thibaut, F., Martinez, M., Samolyk, D., Petit, M., Campion, D., & Mallet, J. (1999). Linkage disequilibrium on the COMT gene in French schizophrenics and controls. American Journal of Medical Genetics, 88, 452-457.

Deicken, R. F., Zhou, L., Corwin, F., Vinogradov, S. Weiner, M. W. (1997). Decreased left frontal lobe N-acetylaspartate in schizophrenia. American Journal of Psychiatry, 154, 688-690.

Demers, R. G. & Heninger, G. R. (1971). Visual-motor performance during lithium treatment- a preliminary report. Journal of Clinical Pharmacology and New Drugs, 11, 274-279.

Detera-Wadleigh, S. D., Badner, J. A., Berrettini, W. H., Yoshikawa, T., Goldin, L. R., Turner, G., Rollins, D. Y., Moses, T., Sanders, A. R., Karkera, J. D., Esterling, L. E., Zeng, J., Ferraro, T. N., Guroff, J. J., Kazuba, D., Maxwell, M. E., Nurnberger Jr., J. I., and Gershon, E. S. (1999). A high-density genome scan detects evidence for a bipolar

disorder susceptibility locus on 13q32 and other potential loci on 1q32 and 18p11.2. Proceedings of the National Academy of Sciences USA, 96, 5604-5609.

Edenberg, H. J., Foroud, T., Conneally, P. M., Sorbel, J. J., Carr, K., Crose, C., Willig, C., Zhao, J., Miller, M., Bowman, E., Mayeda, A., Rau, L., Smiley, C., Rice, J. P., Goate, A. P., Reich, T., Stine, O. C., McMahon, F., DePaulo, J. R., Meyers, D., Detera-Wadleigh, S. D., Goldin, L. R., Gershon, E. S., Blehar, M. C., & Nurnberger, Jr., J .I. (1997). Initial genomic scan of the NIMH genetics initiative bipolar pedigrees: Chromosomes 3, 5, 15, 16, 17, 22. American Journal of Medical Genetics, 74(3), 238-246.

D'Esposito, M., Aguirre, G. K., Zarahn, E., Ballard, D., Shin, R. K., & Lease, J. (1998). Functional MRI studies of spatial and nonspatial working memory. Cognitive Brain Research, 7, 1-13.

D'Esposito, M., Postle, B. R., Ballard, D., & Lease, J. (1999). Maintenance versus manipulation of information held in working memory: An event-related fMRI study. Brain and Cognition, 41(1), 66-86.

D'Esposito, M., Postle, B. R., & Rypma, B. (2000). Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. Experimental Brain Research, 133, 3-11.

Diamond, A., Briand, L., Fossella, J., & Gehlbach, L. (2004). Genetic and neurochemical modulation of prefrontal cognitive functions in children. American Journal of Psychiatry, 161(1), 125-132.

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

Diaz-Asper, C. M., Goldberg, T. E., Kolachana, B. S., Straub, R. E., Egan, M. F., & Weinberger, D. R. (2008). Genetic variation in catechol-O-methyltransferase: Effects on working memory in schizophrenia patients, their siblings, and healthy controls. Biological Psychiatry, 63, 72-79.

Egan, M. F., Goldberg, T. E., Gschiedle, T., Weirich, M., Rawlings, R., Hyde, T. M., Bigelow, L., & Weinberger, D. R. (2001). Relative risk for cognitive impairment in siblings of patients with schizophrenia. Biological Psychiatry, 50, 98-107.

Egan, M. F., Goldberg, T. E., Kolachana, B. S., et al. (2001), Effect of COMT Val108/158Met genotype on frontal lobe function and risk for schizophrenia. Proceedings of the National Academy of Sciences USA, 98(12), 6917-6922.

Elsworth, et al. (1997). Homovanillic acid concentrations in brain, CSF, and plasma as indicators of central dopamine function in primates. Journal of Neural Transmission, 68, 51-62.

Everling, S., Krappman, P., Preuss, S., Brand, A., & Flohr, H. (1998). Hypometric primary saccades of schizophrenics in a delayed response task. Experimental Brain Research, 111, 289-295.

Fan, J. B., Chen, W. Y., Tang, J. X., Li, S., Gu, N. F., Feng, G. Y., Breen, G., St. Clair, D., & He, L. (2002). Family-based association studies of COMT gene

polymorphisms and schizophrenia in the Chinese population. Molecular Psychiatry, 7, 446-452.

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

Ferrier, I. N., Chowdhury, R., Thompson, J. M., Watson, S., & Young, A. H. (2004). Neurocognitive function in unaffected first-degree relatives of patients with bipolar disorder: a preliminary report. Bipolar Disorders, 6, 319-322.

Ferrier, I. N., Stanton, B. R., Kelly, T. P., & Scott, J. (1999). Neuropsychological function in euthymic patients with bipolar patients. British Journal of Psychiatry, 175, 246-251.

Ferrier, I. N. & Thompson, J. M. (2002) Cognitive impairment in bipolar affective disorder: implications for the bipolar diathesis. British Journal of Psychiatry, 180, 293-295.

Finkelstein, J. R. (1998). Attention deficits in schizophrenia: Endophenotypic markers of vulnerability to the disorder? (Doctoral dissertation, University of Pennsylvannia, 1998).

Funahashi, S., Bruce, C. J., Goldman-Rakic, P. S. (1989). Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. Journal of Neurophysiology, 61(2), 331-349.

Funahashi, S., Bruce, C. J., Goldman-Rakic, P. S. (1991). Neuronal activity related to saccadic eye movements in the monkey's dorsolateral prefrontal cortex. Journal of Neurophysiology, 65, 1464-1483.

Galderisi, S., Maj, M., Kirkpatrick, B., Piccardi, P., Mucci, A., Invernizzi, G., Rossi, A., Pini, S., Vita, A., Cassano, P., Stratta, P., Severino, G., & Del Zompo, M. (2005). Catechol-o-methyltransferase Val158Met polymorphism in schizophrenia: Associations with cognitive and motor impairment. Neuropsychobiology, 52, 83-89.

Ganzevles, P. G. J., & Haenen, M. –A. (1995). A preliminary study of externally and self-ordered task performance in schizophrenia. Schizophrenia Research, 16, 67-71.

Gasparini, et al (1997). Cognitive improvement during Tolcapone treatment in Parkinson's disease. Journal of Neural Transmission, 104, 887-894.

George, D. & Mallery, P. (2001). SPSS for windows step by step. Needham Heights: Allyn and Bacon.

Glahn, D. C., Bearden, C. E., Cakir, S., Barrett, J. A., Najt, P., Monkul, E. S., Maples, N., Velligan, D. I., & Soares, J. C. (2006). Differential working memory impairment in bipolar disorder and schizophrenia: effects of lifetime history of psychosis. Bipolar Disorders, 8, 117-123.

Glahn, D. C., Kim, J., Cohen, M. S., Poutanen, V. P., Therman, S., Bava, S., Van Erp, T. G. Manninen, M., Huttunen, M., Lonnqvist, J., Standertskjold-Nordenstam, C. G., & Cannon, T. D. (2002). Maintenance and manipulation in spatial working memory: dissociations in the prefrontal cortex. Neuroimaging, 17, 201-213.

Glahn, D. C., Therman, S., Manninen, M., Huttunen, M., Kaprio, J., Lonnqvist, J., & Cannon, T. D. (2003). Spatial working memory as an endophenotype for schizophrenia. Biological Psychiaty, 53, 624-626.

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

Gochman, P. A., Greenstein, D., Sporn, A., Gogtay, N., Nicolson, R., Keller, A., Lenane, M., Brookner, F., & Rapoport, J. L. (2004). Childhood onset schizophrenia: familial neurocognitive measures. Schizophrenia Research, 71, 43-47.

Gogos, J. A., Morgan, M., Luine, V. Santha, M., Owaga, S., Pfaff, D., & Karayiorgou, M. (1998). Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. Proceedings of the National Academicy of Sciences USA, 95, 9991-9996.

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

Goldberg, T. E. (1999). Some fairly obvious distinctions between sz and bipolar disorder. Schizophrenia Research, 39, 127-132.

Goldberg, T. E., Aloia, M. S., Gourovitch, M. L., Missar, D., Pickar, D., & Weinberger, D. R. (1998). Cognitive substrates of thought disorder, I: The semantic system. American Journal of Psychiatry, 155(12), 1671-1676.

Goldberg, T.E., Egan, M.F., Gscheidle, T., et al). (2003). Executive subprocesses in working memory: Relationship to catechol-O-methyltransferase Val 158Met genotype and schizophrenia. Archives of General Psychatiry, 60, 889-896.

Goldberg, T. E., Ragland, J. D., Torrey, E. F., Gold, J. M., Bigelow, L. B., & Weinberger, D. R. (1990). Neuropsychological assessment of monozygotic twins discordant for schizophrenia. Archives of General Psychiatry, 47, 1066-1072.

Goldberg, T. E., Torrey, E. F., Gold, J. M., Bigelow, L. B., Ragland, R. D., Taylor, E., & Weinberger, D. R. (1995). Genetic risk for neuropsychological impairment in schizophrenia: a study of monozygotic twins discordant and concordant for the disorder. Schizophrenia Research, 17, 77-84.

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

Goldman-Rakic, P. S. (1995). Architecture of the prefrontal cortex and the central executive. Annals of the New York Academy of Sciences, 769, 71-83.

Goldman-Rakic, P. S. (1996). Regional and cellular fractionation of wm. Proceedings of the National Academy of Sciences, 93, 13473-13480.

Goldman-Rakic, P. S. (1999a). The relevance of the dopamine-D1 receptor in the cognitive symptoms of schizophrenia. Neuropsychopharmacology, 21(6), S170-S180.

Goldman-Rakic, P. S. (1999b). The physiological approach: Functional architecture of working memory and disordered cognition in schizophrenia. Biological Psychiatry, 46, 650-661.

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

Gooding, D. C., & Tallent, K. A. (2001). The association between antisaccade task and working memory task performance in schizophrenia and bipolar disorder. Journal of Nervous and Mental Disease, 189(1), 8-16.

Gottesman, I. I. (1991). Schizophrenia genesis: The origins of madness. New York: W. H. Freeman & Co.

Gottesman, I. I., & Bertelsen, A. (1989). Confirming unexpressed genotypes for schizophrenia: Risks in the offspring of Fischer's Danish identical and fraternal discordant twins. Archives of General Psychiatry, 46, 867-872.

Gourovitch, M. L., Torrey, E. F., Gold, J. M., Randolph, C., Weinberger, D. R., & Goldberg, T. E. (1999). Neuropsychological performance of monozygotic twins discordant for bipolar disorder. Biological Psychiatry, 45, 639-646.

Harrison, P. J., & Weinberger, D. R. (2004). Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Molecular Psychiatry, 1-29.

Harmer, C. J., Clark, L., Grayson, L., & Goodwin, G. M. (2002). Sustained attention deficit in bipolar disorder is not a working memory impairment in disguise. Neuropsychologia, 40, 1586-1590.

Hawkins, K. A., Hoffman, R. E., Quinlan, D. M., Rakfeldt, J., Docherty, N.M., Sledge, W.H. (1997). Cognition, negative symptoms, and diagnosis: a comparison of

schizophrenic, bipolar, and control samples. Journal of Neuropsychiatry and Clinical Neurosciences, 9(1), 81-89.

Heydebrand, G. (2006). Cognitive deficits in the families of patients with schizophrenia. Current Opinion in Psychiatry, 19, 277-281.

Hill, K., Mann, L., Laws, K. R., Stephenson, C. M. E., Nimmo-Smith, I., & McKenna, P. J. (2004). Hypofrontality in schizophrenia: a meta-analysis of functional imaging studies. Acta Psychiatrica Scandinavica, 110, 243-256.

Ho, B., Wassink, T. H., O'Leary, D. S., Sheffield, V. C., & Andreasen, N. C. (2005). Catechol-O-methyl transferase val158met gene polymorphism in schizophrenia: working memory, frontal lobe MRI morphology and frontal cerebral blood flow. Molecular Psychiatry, 10, 287-298.

Hoff, A.L., Shukla, S., Aronson, T. et al. (1990). Failure to differentiate bipolar disorder from sz on measures of neurospych function. Schizophrenia Research, 3(4), 253-260.

Hofer, A., & Weiss, E. M. (2002). Advances in the neuroimaging of cognitive functions in schizophrenia. Current Opinion in Psychiatry, 15(1), 3-7.

Holmes, A. J., MacDonald, A., Carter, C. S., Barch, D. M., Stenger, V. A., & Cohen, J .D. (2005) Prefrontal functioning during context processing in schizophrenia and major depression: An event-related fMRI study. Schizophrenia Research, 76, 199-206.

Horowitz, A., Shifman, S., Rivlin, N., Pisante, A., & Darvasi, A. (2005). Further tests of the association between schizophrenia and single nucleotide polymorphism

markers at the catechol-O-methyltransferase locus in Askenazi Jewish population using microsatellite markers. Psychiatric Genetics, 15(3), 163-169.

Inada, T., Nakamura, A., & Iijima, Y. (2003). Relationship between catechol-O-methyltransferase polymorphism and treatment-resistant schizophrenia. American Journal of Medical Genetics, 120B, 35-39.

Ismail, B., Cantor-Graae, E., & McNiel, T. F. (2000). Minor physical anomalies in schizophrenia: cognitive, neurological and other clinical correlates. Journal of Psychiatric Research, 81, 217-226.

Joo, E. –J., Jeong, S. –H., Ahn, Y. –M., Lee, K. –Y., Yoon, S. –C., Kim, E. –J., Kim, S. –U., Cho, S. –C., & Kim, Y. S. (2005). No association found between 158val/met polymorphism of the COMT gene and schizophrenia with minor physical anomalies. Psychiatry Research, 136, 83-91.

Joober, R., Gauthier, J., Lal, S., Bloom, D., Lalonde, P., Rouleau, G., Benkelfat, C., & Labelle, A. (2002), Catechol-o-methyltransferase Val-108/158-Met gene variants associated with performance on the Wisconsin Card Sorting Test. Archives of General Psychiatry, 59, 662-664.

Karatekin, C., & Asarnow, R. F. (1998). Working memory in childhood-onset schizophrenia and attention-deficit/hyperactivity disorder. Psychiatry Research, 80, 165-176.

Karayiorgou, M., Altemus, M., Galke, B. L., Goldman, D., Murphy, D. L., Ott, J., & Gogos, J. A. (1997). Genotype determining low catechol-O-methyltransferase activity

as a risk factor for obsessive-compulsive disorder. Proceedings of the National Academy of Sciences, 94, 4572-4575.

Karayiorgou, M., Gogos, J. A., Galke, B. L., Wolyniec, P. S., Nestadt, G., Antonarakis, S. E., Kazazian, H. H., Housman, D. E., & Pulver, A. E. (1998). Identification of sequence variants and analysis of the role of the catechol-O-methyltransferase gene in schizophrenia susceptibility loci. Biological Psychiatry, 43, 425-431.

Karayiorgou, M., Sobin, C., Blundell, M. L., Galke, B. L., Malinova, L., Goldberg, P., Ott, J., & Gogos, J. A. (1999). Family-based association studies support a sexually dimorphic effect of COMT and MAOA on genetic susceptibility to obsessive-compulsive disorder. Biological Psychiatry, 45, 1178-1189.

Karoum, F et al. (1994). 3-Methoxytyramine is the major metabolite of released dopamine in the rat frontal cortex: Reassessment of the effects of antipsychotics on the dynamics of dopamine release and metabolism in the frontal cortex, nucleus accumbens, and striatum by a s simple two pool model. Journal of Neurochemistry, 63, 972-979.

Keefe, R. S. E., Roitman, S. E. L., Harvey, P. D., Blum, C. S., DuPre, R. L., Prieto, D. M., Davidson, M., & Davis, K. L. (1995). A pen-and-paper human analogue of a monkey prefrontal cortex activation task: spatial working memory in patients with schizophrenia. Schizophrenia Research, 17, 25-33.

Kendler, K. S., & Eaves, L. (2005). Psychiatric Genetics. Washington, D. C.: American Psychiatric Publishing.

Keri, S., Kelemen, O., Benedek, G., & Janka, Z. (2001). Different trait markers for schizophrenia and bipolar disorder: a neurocognitive approach. Psychological Medicine, 31, 915-922.

Keshavan, M. S., Diwadkar, V. A., Spencer, S. M., Harenski, K. A., Luna, B., & Sweeney, J. A. (2002). A preliminary functional magnetic resonance imaging study in offspring of schizophrenia parents. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 26, 1143-1149.

Kiefer, M., Apel, A., & Weisbrod, M. (2002). Arithmetic fact retrieval and working memory in schizophrenia. Schizophrenia Research, 53, 219-227.

Kieseppa, T., Tuulio-Henriksson, A., Haukka, J., Van Erp, T., Glahn, D., Cannon, T., Partonen, T., Kaprio, J., & Lonnqvist, J. (2004). Memory and verbal learning functions in twins with bipolar-I disorder, and the role of information-processing speed. Psychological Medicine, 35, 205-215.

Kim, J., Glahn, D. C., Nuechterlein, K. H., & Cannon, T. D. (2004). Maintenance and manipulation of information in schizophrenia: further evidence for impairment in the central executive component of working memory. Schizophrenia Research, 68, 173-187.

Krappmann, P., & Everling, S. (1998). Spatial accuracy of primary and secondary memory-guided saccades in schizophrenic patients. Schizophrenia Research, 30, 183-185.

Kremer, I., Pinto, M., Murad, I., Muhaheed, M., Bannoura, I., Muller, D. J., Schulze, T. G., Reshef, A., Blanaru, M., Gathas, S., Goichman, R. Rietschel, M.,

Dobrusin, M., Bachner-Melman, R., Nemanov, L., Belmaker, R. H., Maier, W., & Ebstein, R. P. (2003). Family-based and case-control study of catechol-O-methyltransferase in schizophrenia among Palestinian Arabs. American Journal of Medical Genetics, 119B, 35-39.

Kunugi, H., Vallada, H. P., Sham, P. C., Hoda, F., Arranz, M. Z., Li, T., Nanko, S., Murray, R. M., McGuffin, P., Owen, M., & Gill, M. (1997). Catechol-O-methyltransferase polymorphisms and schizophrenia: A transmission disequilibrium study in multiply affected families. Psychiatric Genetics, 7(3), 97-101.

Kusumo, K. S., & Vaughan, M. (1977). Effects of lithium salts on memory. British Journal of Psychiatry, 131, 453-457.

Lachman, H. M., Morrow, B., Shprintzen, R., Veit, S., Parsia, S. S., Faedda, G., Goldberg, R., Kucherlapati, R., & Papolos, D. F. (1996). Association of codon 108/158 catechol-O-methyltransferase gene polymorphism with the psychiatric manifestations of Velo-Cardio-Facial Syndrome. American Journal of Medical Genetics, 67, 468-472.

Laurent, A., Moreaud, O., Bosson, J. –L., Naegele, B., Boucharlat, J., Saoud, M., Dalery, J., & d'Amato, T. (1999). Neuropsychological functioning among non-psychotic siblings and parents of schizophrenic patients. Psychiatry Research, 87, 147-157.

Leiderman, E. A., & Strejilevich, S. A. (2004). Visuospatial deficits in schizophrenia: central executive and memory subsystems impairments. Schizophrenia Research, 68, 217-223.

Lewis, D. A. (1997). Development of the prefrontal cortex during adolescence: Insights into vulnerable neural circuits in schizophrenia. Neuropsychopharmacology, 16, 385-398.

Lewis, C. M., Levinson, D. F., Wise, L. H., DeLisi, L. E., Straub, R. E., et al. (2003). Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. American Journal of Human Genetics, 73, 34-48.

Li, T., Ball, D., Zhao, J., Murray, R. M., Liu, X., Sham, P. C., & Collier, D. A. (2000). Family-based linkage disequilibrium mapping using SNP marker haplotypes: application to a pontential locus for schizophrenia at chromosome 22q11. Molecular Psychiatry, 5, 77-84.

Li, T., Sham, P. C., Vallada, H., Xie, T., Tang, X., Murray, R. M., Liu, X., & Collier, D. A. (1996). Preferential transmission of the high activity allele of COMT in schizophrenia. Psychiatric Genetics, 6(3), 131-133.

Lijequist, R., Haapalinna, A., Ahlander, M., Li, Y. H., & Mannisto, P. T. (1997). Catechol-O-methyltransferase inhibitor tolcapone has minor influence on performance in experimental memory models in rats. Behavioural Brain Research, 82, 195-202.

Liou, Y. –J., Tsai, S. –J., Hong, C. –H., Wang, Y. –C., & Lai, I. –C. (2001) Association analysis of a functional catechol-O-methyltransferase gene polymorphism in schizophrenic patients in Taiwan. Neuropsychobiology, 43, 11-14.

Mahurin, R. K., Velligan, D. I., & Miller, A. L. (1998). Executive-frontal lobe cognitive dysfunction in schizophrenia: A symptom subtype analysis. Psychiatry Research, 79, 139-149.

MacDonald III, A. W., & Carter, C. S. (2003). Event-related fMRI study of context processing in dorsolateral prefrontal cortex of patients with schizophrenia. Journal of Abnormal Psychology, 112(4), 689-697.

MacDonald III, A. W., Carter, C. S., Kerns, J . G., Ursu, S., Barch, D. M., Holmes, A. J., Stenger, V. A., & Cohen, J. D. (2005). Specificity of prefrontal dysfunction and context processing deficits to schizophrenia in never-medicated patients with first-episode psychosis. American Journal of Psychiatry, 162(3), 475-484.

Maier, W., Hofgen, B., Zobel, A., & Rietschel, M. (2005). Genetic models of schizophrenia and bipolar disorder: Overlapping inheritance or discrete genotypes? European Archives of Psychiatry and Clinical Neuroscience, 255, 159-166.

Malhotra, A. K., Kestler, L. J., Mazzanti, C., Bates, J. A., Goldberg, T., & Goldman, D. (2002). A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. American Journal of Psychiatry, 159(4), 652-654.

Manoach, D. S., Press, D. Z., Thangaraj, V., Searl, M. M., Goff, D. C., Halpern, E., Saper, C. B., & Warach, S. (1999). Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. Biological Psychiatry, 45, 1129-1137.

Matsumoto, M. Weickert, C. S., Akil, M., Lipska, B. K., Hyde, T. M., Herman, M. M., Kleinman, J. E., & Weinberger, D. R. (2003). Catechol-O-methyltransferase m RNA expression in human and rat brain: evidence for a role in cortical neuronal function. Neuroscience, 116, 127-137.

McDowell, J. E., Brenner, C. A., Myles-Worsely, M., Coon, H., Byerley, W., & Clementz, B. A. (2001). Ocular motor delayed-response task performance among patients with schizophrenia and their biological relatives. Psychophysiology, 38, 153-156.

McDowell, J. E., & Clementz, B. A. (1996). Ocular-motor delayed-response task performance among schizophrenia patients. Neuropsychobiology, 34, 67-71.

McGue, M., Gottesman, I. I., & Rao, D. C. (1985). Resolving genetic models for the transmission of schizophrenia. Genetic Epidemiology, 2, 99-110.

McGurk, S. R., Coleman, T., Harvey, P. D., Reichenberg, A., White, L., Friedman, J., Parrella, M., & Davis, K. L. (2004). Working memory performance in poor outcome schizophrenia: Relationship to age and executive functioning. Journal of Clinical and Experimental Neuropsychology, 26(2), 153-160.

Meehl, P. E. (1971). High school yearbooks: A reply to Schwarz. Journal of Abnormal Psychology, 77(2), 143-148.

Mellers, J. D. C., Toone, B. K., & Lishman, W. A. (2000). A neuropsychological comparison of schizophrenia and schizophrenia-like psychosis of epilepsy. Psychological Medicine, 30, 325-335.

Meyer-Lindenberg, A., Nichols, T., Callicott, J. H., Ding, J., Kolachana, B., Buckholtz, J., Mattay, V. S., Egan, M., & Weinberger, D. R. (2006). Impact of complex genetic variation in *COMT* on human brain function. Molecular Psychiatry, 11, 867-877.

Miller, W. R. (1975). Psychological deficit in depression. Psychological Bulletin, 82, 238-260.

Minor, K. & Park, S. (1999). Spatial working memory: Absence of gender differences in schizophrenia patients and healthy control subjects. Biological Psychiatry, 46, 1003-1005.

Minzenberg, M. J., Xu, K., Mitropoulou, V., Harvey, P. D., Finch, T., Flory, J. D., New, A. S., Goldman, D., & Siever, L. J. (2006). Catechol-O-methyltransferase Val158Met genotype variation is associated with prefrontal-dependent task performance in schizotypal personality disorder patients and comparison groups. Psychiatric Genetics, 16(3), 117-124.

Monks, P. J., Thompson, J. M., Bullmore, E. T., Suckling, J., Brammer, M. J., Williams, S. C. R., Simmons, A., Giles, N., Lloyd, A. J., Harrison, C. L., Seal, M., Murray, R. M., Ferrier, I. N., Young, A. H., & Curtis, V. A. (2004). A functional MRI study of working memory task in euthymic bipolar disorder: evidence for task-specific dysfunction. Bipolar Disorders, 6, 550-564.

Morey, R. A., Inan, S., Mitchell, T. V., Perkins, D. O., Lieberman, J . A., & Belger, A. (2005). Imaging frontostriatal function in ultra-high-risk, early, and chronic schizophrenia during executive processing. Archives of General Psychiatry, 62, 254-262.

Moritz, S., Birkner, C., Kloss, M., Jahn, H., Hand, I., Haasen, C., & Krausz, M. (2002). Executive functioning in obsessive-compulsive disorder, unipolar depression, and schizophrenia. (2002). Archives of Clinical Neuropsychology, 17, 477-483.

Mujaheed, M., Corbex, M., Lichtenberg, P., Levinson, D. F., Deleuze, J. F., Mallet, J., & Ebstein, R. P. (2000). Evidence for linkage by transmission disequilibrium

test analysis of a chromosome 22 microsatellite marker D22S278 and bipolar disorder in a Palestinian Arab population. American Journal of Psychiatry, 148, 612-616.

Muller, U., Werheid, K., Hammerstein, E., Jungmann, S., & Becker, T. (2005). Prefrontal cognitive deficits in patients with schizophrenia treated with atypical or conventional antipsychotics. European Psychiatry, 20, 70-73.

Munafo, M. R., Bowes, L., Clark, T. G., & Flint, J. (2005). Lack of association of the COMT (val158/108met) gene and schizophrenia: a meta-analysis of case-control studies. Molecular Psychiatry, 10, 765-770.

Ophoff, et al. (2002). Genomewide linkage disequilibrium mapping of severe bipolar disorder in population isolate. American Journal of Human Genetics, 71, 565-574.

Pae, C. U., Choe, B. Y., Joo, R. H., Lim, H. K., Kim, T. S., Yoo, S. S., Choi, B. G., Kim, J. J., Lee, S. J., Lee, C., Paik, I. H., & Lee, C. U. (2004). Neuronal dysfunction of the frontal lobe in schizophrenia. Biological Psychiatry, 50, 211-215.

Palmatier et al (1999). Global variation in the frequencies of functionally different Catechol-O-methyltransferase alleles. Biological Psychiatry, 46, 557-567.

Papageorgiou, C., Lykouras, L., Alevizos, B., Ventouras, E., Mourtzouchou, P., Uzunoglu, N., Christodoulou, G. N., & Rabavilas, A. (2005). Psychophysiological differences in schizophrenics with and without delusional misidentification syndromes: A P300 study. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 29, 593-601.

Park, S. (1997). Association of an oculomotor delayed response task and the Wisconsin Card Sort Test in schizophrenia patients. International Journal of Psychophysiology, 27, 147-151.

Park, S. (1999). Hemispheric asymmetry of spatial working memory deficit in schizophrenia. International Journal of Psychophysiology, 34, 313-322.

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

Park, S., & Holzman, P. S. (1993). Association of working memory deficit and eye tracking dysfunction in schizophrenia. Schizophrenia Research, 11, 55-61.

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

Park, S., Puschel, J., Sauter, B. H., Rentsch, M., & Hell, D. (1999). Spatial working memory deficits and clinical symptoms in schizophrenia: A 4-month follow-up study. Biological Psychiatry,46, 392-400.

Partiot, A., Jouvent, R., Dubois, B., Verin, M., Montreuil, M., Agid, Y., & Widlocher, D. (1992). European Psychiatry, 7, 171-175.

Perlman, W. R., Weickert, C. S., Akil, M., & Kleinman, J. E. (2004). Postmortem investigations of the pathophysiology of schizophrenia: the role of susceptibility genes. Journal of Psychiatry Neuroscience, 29(4), 287-293.

Perlstein, W. M., Dixit, N. K., Carter, C. S., Noll, D. C., & Cohen, J .D. (2003). Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. Biological Psychiatry, 53(1), 25-38.

Potash, et al. (2003). Suggestive linkage to chromosomal regions 13q31 and 22q12 in families with psychotic bipolar disorder. American Journal of Psychiatry, 160, 680-686.

Postle, B. R., Berger, J. S., D'Esposito, M. (1999). Functional neuroanatomical double dissociation of mnemonic and executive control processes contributing to working memory performance. Proceedings of the National Academy of Sciences USA, 96, 12959-12964.

Pukrop, R., Matuschek, E., Ruhrmann, S., Brockhaus-Dumke, A., Tendolkar, I., Bertsch, A., & Klosterkotter, J. (2003). Dimensions of working memory dysfunction in schizophrenia. Schizophrenia Research, 62, 259-268.

Quraishi, S., & Frangou, S. (2002). Neurospychology of bipolar disorder: a review. Journal of Affective Disorders, 72(3), 209-226.

Raine, A., Lencz, T., Reynolds, G. P., Harrison, G., Sheard, C., Medley, I., Reynolds, L. M., & Cooper, J. E. (1992). An evaluation of structural and functional prefrontal deficits in schizophrenia: MRI and neuropsychological measures. Psychiatry Research, 45, 123-137.

Risch, N. (1990). Linkage strategies for genetically complex traits: I. Multi-locus models. American Journal of Human Genetics, 46, 222-228.

Risch, N., & Merikangas, K. (1996). The future of genetic studies of complex human diseases. Science, 273, 1516-1517.

Roffman, J. L., Gollub, R. L., Calhoun, V. D., Wassink, T. H., Weiss, A. P., Ho, B. C., White, T., Clark, V. P., Fries, J., Andreasen, N. C., Goff, D. C., & Manoach, D. S. (2008). MTHRF 677C→T genotype disrupts prefrontal function in schizophrenia through an interaction with COMT 158Val→Met. Proceedings of the National Academy of Sciences, 105(45), 17573-17578.

Rolink, J. D., Borsutzky, M., Huber, T., Mogk, H., Seifert, J., Emrich, H. M., & Schneider, U. (2002). Short-term cognitive improvement in schizophrenics treated with typical and atypical neuroleptics. Neuropsychobiology, 45, 74-80.

Rosa, A., Peralta, V., Cuesta, M. J., Zarzuela, A. Serrano, F., Martinez-Larrea, A., & Fananas, L. (2004). New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. American Journal of Psychiatry, 161(6), 1110-1112.

Ross, R. G., Harris, J. G., Olincy, A., & Radant, A. (2000). Eye movement task measures inhibition and spatial working memory in adults with schizophrenia, ADHD, and a normal comparison group. Psychiatry Research, 95, 35-42.

Ross, R. G., Harris, J. G., Olincy, A., Radant, A., Adler, L. E., & Freedman, R. (1998). Familial transmission of two independent saccadic abnormalities in schizophrenia. Schizophrenia Research, 30, 59-79.

Rotondo, A., Mazzanti, C., Dell'Osso, L., Rucci, P., Sullivan, P., Bouanani, S., Gonnelli, C., Goldman, D., Cassano, G. B. (2002). Catechol-O-methyltransferase,

serotonin transporter, and trypophan hydroxylase gene polymorphisms in bipolar disorder patients with and without comorbid panic disorder. American Journal of Psychiatry, 159, 23-29.

Rujescu, D., Giegling, I., Gietl, A., Hartmann, A. M., & Moller, H. –J. (2003). A functional single nucleotide polymorphism (v158m) in the COMT gene is associated with aggressive personality traits. Biological Psychiatry, 54, 34-39.

Salame, P., Danion, J. –M., Peretti, S., & Cuervo, C. (1998). The state of functioning of working memory in schizophrenia. Schizophrenia Research, 30, 11-29.

Schubert, E. W. & McNeil, T. F. (2005). Neuropsychological impairment and its neurological correlates in adult offspring with heightened risk for schizophrenia and affective psychosis. American Journal of Psychiatry, 162, 758-766.

Seidman, L. J., Kremen, W. S., Koren, D., Faraone, S. V., Goldstein, J. M., & Tsuang, M. T. (2002). A comparative profile analysis of neuropsychological functioning in patients with sz and bipolar psychoses. Schizophrenia Research, 53, 31-44.

Seidman, L. J., Oscar-Berman, M., Kalinowski, A. G., Ajilore, O., Kremen, W. S., Faraone, S. V., & Tsuang, M. T. (1995). Neuropsychology, 9(4), 481-490.

Selemon, L. D., & Goldman-Rakic, P. S. (1999). The reduced neuropil hypothesis: A circuit based model of schizophrenia. Biological Psychiatry, 45, 17-25.

Selemon, L. D., Rajkowska, G., Goldman-Rakic, P. S. (1995). Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. Archives of General Psychiatry, 52, 805-818.

Semwal, P., Prasad, S., Bhatia, T., Deshpande, S. N., Wood, J., Nimgaonkar, V. L., & Thelma, B. K. (2001). Family-based association studies of monoaminergic gene polymorphisms among North Indians with schizophrenia. Molecular Psychiatry, 6, 220-224.

Shedlack, K., Lee, G., Sakuma, M., Xie, S. –H., Kushner, M., Pepple, J., Finer, D. L., Hoff, A. L., & DeLisi, L. E. (1997). Language processing and memory in ill and well siblings from multiplex families affected with schizophrenia. Schizophrenia Research, 25, 43-52.

Shield, A. J., Thomae, B. A., Eckloff, B. W., Wieben, E. D., & Weinshilboum, R. M. (2004). Human catechol-O-methyltransferase genetic variation: gene resequencing and functional characterization of variant allozymes. Molecular Psychiatry, 9, 151-160.

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

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

Silver, H., Feldman, P., Bilker, W., & Gur, R. C. (2003). Working memory deficit as a core neuropsychological dysfunction in schizophrenia. American Journal of Psychiatry, 160, 1809-1816.

Smith, C. W., Park, S., & Cornblatt, B. (2006). Spatial working memory deficits in adolescents at clinical high risk for schizophrenia. Schizophrenia Research, 81, 211-215.

Smyrnis, N., Avrampoulous, D., Evdokimidis, I., Stefanis, C. N., Tsekou, H., & Stefanis, N. C. (2007). Effect of schizotypy on cognitive performance and its tuning by COMT val158met genotype variations in a large population of young men. Biological Psychiatry, 61,Biological Psychiatry, 61, 845-853.

Snitz, B. E., Curtis, C. E., Zald, D. H., Katsanis, J., & Iacono, W. G. (1999). Neurospychological and oculomotor correlates of spatial working memory performance in schizophrenia patients and controls. Schizophrenia Research, 38, 37-50.

Snitz, B. E., MacDonald III, A. W., and Carter, C. S. (2006). Cogntiive deficits in unaffected first-degree relatives of schizophrenia patients: A meta-analytic review of putative endophenotypes. Schizophrenia Bulletin, 32(1), 79-194.

Spindler, K. A., Sullivan, E. V., Menon, V., Lim, K. O., & Pfefferbaum, A. (1997). Deficits in multiple systems of working memory in schizophrenia. Schizophrenia Research, 27, 1-10.

Sponheim, S. R., Iacono, W. G., Thuras, P. D., & Beiser, M. (2001). Using biological indicies to classify schizophrenia and other psychotic patients. Schizophrenia Research, 50, 139-150.

Staal, W. G., Hijman, R., Hulshoff Pol, H. E., Kahn, R. S. (2000). Neuropsychological dysfunctions in siblings discordant for schizophrenia. Psychiatry Research, 95, 227-235.

Stefansson, S. B., & Jonsdottir, T. J. (1996). Auditory event-related potentials, auditory digit span, and clinical symptoms in chronic schizophrenic men on neuroleptic medication. Biological Psychiatry, 40, 19-27.

Stone, M. Gabrieli, J. D., Stebbins, G. T., & Sullivan, E. V. (1998). Working and strategic memory deficits in schizophrenia. Neuropsychology, 12(2), 278-288.

Strakowski, S. M., Delbello, M. P., Adler, C., Cecil, K.M., & Sax, K. W. (2000). Neuroimaging in bipolar disorder. Bipolar Disorders, 2, 148-164.

Stratta, P., Daneluzzo, E., Prosperini, P., Bustini, M., Mattei, P., & Rossi, A. (1997). Is Wisconsin Card Sorting Test performance related to 'working memory' capacity? Schizophrenia Research, 27, 11-19.

Stratta, P., Properini, P., Daneluzzo, E., Bustini, M., & Rossi, A. (2001). Educational level and age influence spatial working memory and Wisconsin Card Sorting Test performance differently: a controlled study in schizophrenic patients. Psychiatry Research, 102, 39-48.

Sullivan, P. F., Kendler, K. S., Neale, M. C. (2003). Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry, 60, 1187-1192.

Strous, R. D., Bark, N., Woerner, M., & Lachman, H. M. (1997). Lack of association of a functional catechol-O-methyltransferase gene polymorphism in

schizophrenia. Biological Psychiatry, 41, 493-495.

Sweeney, J. A., Kmiec, J. A., and Kupfer, D. J. (2000). Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. Biological Psychiatry, 48, 674-685.

Tam, W.C., Sewell, K. W., & Deng, H. C. (1998). Information processing in schizophrenia and bipolar disorder: a discriminant analysis. Journal of Nervous and Mental Disease, 186, 597-603.

Tan, H. Y., Chen, Q., Sust, S., Buckholtz, J. W., Meyers, J. D., Egan, M. F., Mattay, V. S., Meyer-Lindenberg, A., Weinberger, D. R., & Callicott, J. H. (2007). Epistasis between catechol-O-methyltransferase and type II metabotropic glutamate receptor 3 genes on working memory brain function. Proceedings of the National Academy of Sciences, 104(30), 12536-12541.

Tan, H., Choo, W., Fones, C. S. L., Chee, M. W. L. (2005). fMRI study of maintenance and manipulation processes within working memory in first-episode schizophrenia. American Journal of Psychiatry, 162(10), 1849-1858.

Thompson, J. M., Ferrier, I . N., Hughes, J. H., et al. (2000). Neurospsychological function in a cohort of bipolar patientss prospectively verified as euthymic. Acta Neuropsychiatrica, 12, 170.

Thompson, J. M., Gallagher, P., Hughes, J. H., Watson, S., Gray, J. M., Ferrier, I. N., Young, A. H. (2005). Neurocognitive impairment in euthymic patients with bipolar affective disorder. The British Journal of Psychiatry, 186, 32-40

Thompson, J. M., Gray, J. M, Ferrier, I. N., Hughes, J. H., Watson, S., & Young, A. H. (2001a). A component process analysis of working memory dysfunction in bipolar patients. Bipolar Disorders, 3, 60.

Thompson, J. M., Gray, J. M., Wilkinson, B., Hughes, J. H., Del-Estal, D., Watson, S., Ferrier, I. N., & Young, A. H. (2001b). Impaired working memory monitoring on the Self-Ordered Pointing Task in euthymic bipolar patients. Journal of Psychopharmacology, 15, A67.

Trandafir, A., Meary, A., Schurhoff, F., Leboyer, M., & Szoke, A. (2006). Memory tests in first-degree adult relatives of schizophrenic patients: A meta-analysis. Schizophrenia Research, 81, 217-226.

Tsai, S. –J., Hong, C. –J., Liao, D. –L., Laio, I. –C., & Liou, Y. –J. (2004). Association study of a functional catechol-O-methyltransferase genetic polymorphism with age of onset, cognitive function, symptomatology, and prognosis in chronic schizophrenia. Neuropsychobiology, 49, 196-200.

Tunbridge, E. M., Harrison, P . J., & Weinberger, D. R. (2006). Catechol-o-methyltransferase, cognition, and psychosis: Val158met and beyond. Biological Psychiatry, 60, 141-151.

Uleland, T., Oie, M., Landro, N. I., & Rund, B. R. (2004). Cognitive functioning in adolescents with schizophrenia spectrum disorders. Psychiatry Research, 126, 229-239.

Van Gorp, W. G., Alshuler, L., Theberge, D. C., Wilkins, J., & Dixon, W. (1998). Cognitive impairment in euthymic bp pts with and without perior alcohol dependence. A preliminary study. Archives of General Psychiatry, 55, 41-46.

Wade, J., Hart, R., Lehman, L, & Hamer, R. (1988). Neurospychological dysfunction in schizophrenia and bipolar disorder. Journal of Clinical and Experimental Neuropsychology, 10, 71.

Wagner, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory: A meta-analysis. Cognitive, Affective, and Behavioral Neuroscience, 3(4), 255-274.

Walter, H., Wunderlich, A. P., Blankenhorn, M., Schafer, S. Tomczak, R., Spitzer, M., & Gron, G. (2003). No hypofrontality, but absence of prefrontal lateralization comparing verbal and spatial working memory in schizophrenia. Schizophrenia Research, 61, 175-184.

Wechsler, D. (1981). The psychometric tradition: Developing the Wechsler Adult Intelligence Scale. Contemporary Educational Psychology. Vol 6(2), 82-85.

Wei, J., & Hemmings, G. P. (2000). Lack of evidence for association between the COMT locus and schizophrenia. Psychiatric Genetics, 9(4),183-186.

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

Weinberger, D. R. (2001). Prefrontal neurons and the genetics of schizophrenia. Biological Psychiatry, 50, 825-844.

Weinberger, D. R. (2005). Genetic Mechanisms of Psychosis: In Vivo and Postmortem Genomics. Clinical Therapeutics, 27, (Supplement A), S8-S15.

Weinberger, D. R. & Berman, K .F. (1986). Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: Regional cerebral blood flow evidence. Archives of General Psychiatry, 43, 114-124.

Williams, H. J., Glaser, B., Williams, N. M., Norton, N., Zammit, S., Macgregor, S., Kirov, G. K., Owen, M. J., & O'Donovan, M. C. (2005). No association between schizophrenia and polymorphisms in COMT in two large samples. American Journal of Psychiatry, 162, 1736-1738.

Wonodi,I., Stine, O. C., Mitchell, B. D., Buchanan, R. W., & Thaker, G. K. (2003). Association between val108/158met polymorphism of the COMT gene and schizophrenia. American Journal of Medical Genetics, 120B, 47-50.

Woo, J. –M., Yoon, K. –S., & Yu, B. –H. (2002). Catechol-O-methyltransferase genetic polymorphism in panic disorder. American Journal of Psychiatry, 159, 1785-1787.

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

Woodward, N. D., Jayathilake, K., & Meltzer, H. Y. (2007). COMT val108-158met genotype, cognitive function, and cognitive improvement with clozapine in schizophrenia. Schizophrenia Research, 90, 86-96.

Xu, H., Kellendonk, C. B., Simpson, E. H., Keilp, J. G., Bruder, G. E., Polan, H. J., Kandel, E. R., & Gilliam, T. C. (2007). DRD2 C957T polymorphism interacts with the COMT Val158Met polymorphism in human working memory ability. Schizophrenia Research, 90, 104-107.

Zalla, T., Joyce, C., Szoke, A., Schurhoff, F., Pillon, B., Komano, O., Perez-Diaz, F., Bellivier, F., Alter, C., Dubois, B., Rouillon, F., Houde, O., Leboyer, M. (2004). Executive dysfunctions as potential markers of familial vulnerability to bipolar disorder and schizophrenia. Psychiatry Research, 121, 207-217.

Zihl, J., Gron, G., Brunnauer, A. (1988). Cognitive deficits in schizohprenia and affective disorders: evidence for a final common pathway disorder. Acta Psychiatrica Scandinavica, 97(5), 351-357.

Zubieta, J. K., Huguelet, P., O'Neil, R. L., Giordani, B. J. (2001). Cognitive function in euthymic bipolar I disorder. Psychiatry Research, 102, 9-20.

Zuffante, P., Leonard, C. M., Kuldau, J. M., Bauer, R. M., Doty, E. G., & Bilder, R. M. (2001). Working memory deficits in schizophrenia are not necessarily specific or associated with MRI-based estimates of area 46 volumes. Psychiatry Research: Neuroimaging Section, 108, 187-209.

Appendix A

Table 1

Demographic Characteristics of Patient Groups and Nonpsychiatric Controls

	Diagnostic Group		
	Schizophrenia (n=59)	Bipolar Disorder (n=31)	Controls (n=66)
Gender (% females)	16.9	22.6	47
Age (in years)			
M	46.2	43.2	43.5
SD	7.7	9.7	9.9
Education (in years)			
M	14.1*	15.3	15.8
SD	2.5	2.2	3.8
IQ			
M	97.3**	111.3	109.6
SD	12.5	17.0	12.7

*p=.003 for difference from nonpsychiatric controls

**p<.0005 for difference from nonpsychiatric controls and bipolar disorder patients

Appendix B

Table 2

Demographic Characteristics of Relative Groups and Nonpsychiatric Controls

	Diagnostic Group		
	Schizophrenia Relatives (n=73)	Bipolar Disorder Relatives (n=28)	Controls (n=69)
Gender (% females)	57.5	46.4	48.5
Age (in years)			
M	49.1	47.3	45.7
SD	8.8	12.8	10.8
Education (in years)			
M	14.7	14	15.3
SD	2.5	3.1	3.8
IQ			
M	105	109.2	109.1
SD	15.2	13.7	12.8

Appendix C

Table 3

Mean Raw Scores and Standard Deviations for Relative Groups and Nonpsychiatric Controls

	SZREL M (SD) N	BPREL M (SD) N	NC M (SD) N	*F*	*p*	η^2	ICC
DRT Combined	13.68[a] (3.6) 66	12.72 (2.9) 26	12.01 (4.1) 47	2.57	.08	.037	.07
DRT Spatial	14.80[b] (4.5) 66	13.08 (3.9) 26	12.81 (4.8) 47	3.11	.05	.044	.07
DRT Verbal	12.57 (3.5) 66	12.35 (3.4) 26	11.21 (4.1) 47	1.94	.15	.028	.00
Self Ordered Pointing	20.63 (7.4) 62	20.28 (6.2) 25	23.26 (9.4) 66	1.89	.15	.025	.17
Digit Span Backward	4.76[c] (1.1) 71	5.04 (1.2) 26	5.46 (1.5) 68	4.77	.01	.057	.42
Letter Number Sequencing	5.10[d] (1.2) 70	5.27 (.9) 26	5.59 (.9) 69	3.69	.03	.044	.43

SZREL=relatives of schizophrenia patients, BPREL=relatives of bipolar disorder patients, NC=nonpsychiatric controls
The *F* statistic is for the group effect. η^2 represents the effect size of group from ANOVA computation. ICC is intraclass correlation reflecting family-level variance adjusted for proband diagnosis. M=Mean, SD=Standard Deviation, N=sample size
DRT Combined data is for average of spatial and verbal interference scores on Spatial Delayed Response Task
[a] paired comparisons difference from nonpsychiatric controls p=.02 for main effect trend of p=.06, [b] p=.02 for difference from nonpsychiatric controls, [c] p=.002 for difference from nonpsychiatric controls, [d] p=.006 for difference from nonpsychiatric controls.

Appendix D

Table 4

Demographic Characteristics of Genotype Groups

	Genotype Group		
	Val/Val (n = 56)	Heterozygote (n = 102)	Met/Met (n = 56)
Gender (% females)	42.9	43.1	30.4
Age (in years)			
M	46.1	46.6	45.9
SD	9.4	9.5	10.4
Education (in years)			
M	15.1	14.4	15.4
SD	4.1	2.6	2.7
IQ			
M	103.4	105.6	107.5
SD	15.9	13.8	15.9

Appendix E

Table 5

Ethnicity of Genotype Groups

	Genotype Group		
	Val/Val (n = 56)	Heterozygote (n = 102)	Met/Met (n = 56)
Anglo Saxon	87%	93.1%	90.7%
Eastern European	0%	3%	3.7%
Russian	0%	0%	1.9%
Mexican Hispanic	1.9%	0%	0%
Native American/Alaska Native	0%	2%	0%
African American	11.1%	2%	1.9%
Other	0%	0%	1.9%

Appendix F

Table 6

Demographic Characteristics of Diagnostic Groups Across Tasks

	Diagnostic Group				
	Nonpsychiatric Controls (n=44)	Schizophrenia Patients (n=36)	Bipolar Disorder Patients (n=29)	Relatives of Schizophrenia (n=61)	Relatives of Bipolar Disorder (n=25)
Gender (% females)	38.6	19.4	24.1	54.1	52.0
Age (in years)					
M	48.3	45.3	43.5	48.6	46.7
SD	10.4	8.5	9.6	8.6	12.2
Education (in years)					
M	15.8	13.8 [1 2 3]	15.2	14.9	14.4 [4]
SD	4.6	2.8	2.2	2.4	2.2
IQ					
M	107.7 [a]	96.8 [b]	111.7 [c]	106.2 [a]	108.5 [a]
SD	11.2	13.1	15.9	14.2	14.1

[1] p=.004 for difference from nonpsychiatric controls, [2] p=.06 for difference from bipolar disorder patients, [3] p=.09 for difference from relatives of schizophrenia patients, [4] p=.07 for difference from nonpsychiatric controls, [a] p=.001 for difference from schizophrenia patients, [b] p<.0005 for difference from bipolar disorder patients, [c] p=.08 compared with relatives of schizophrenia patients

Appendix G

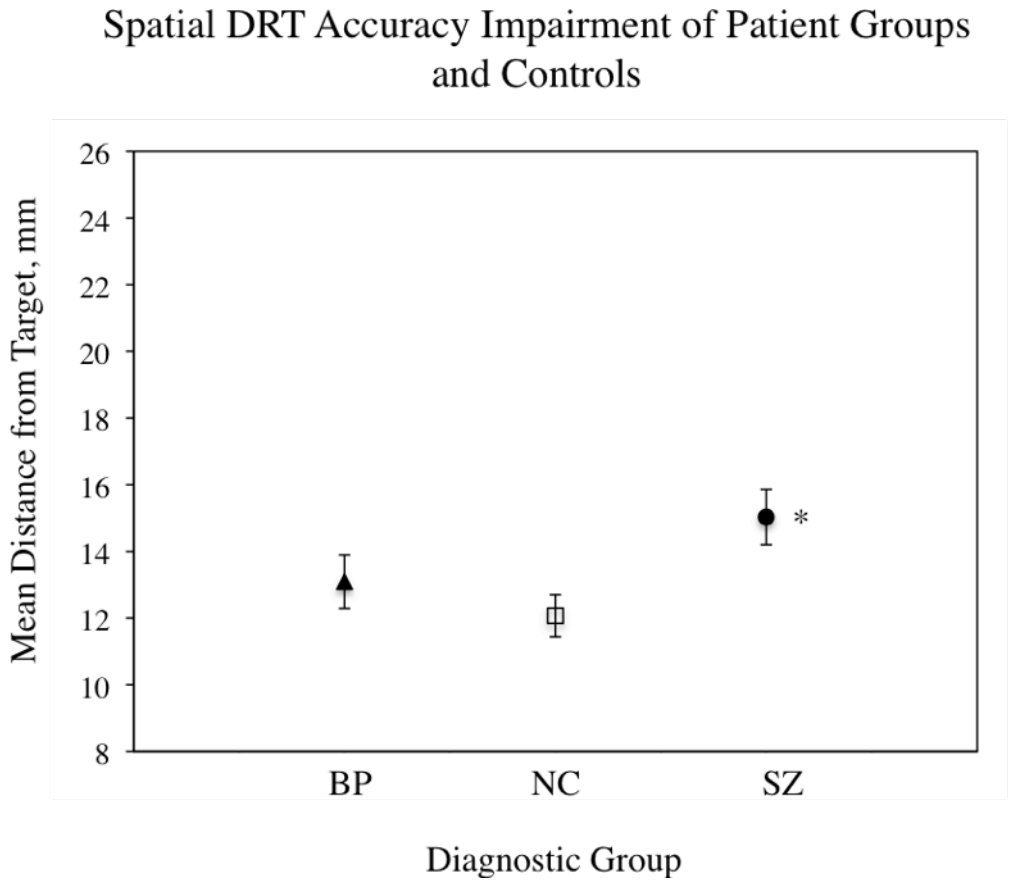

Figure 1. For patient groups and controls, average amount of impairment to accuracy on Spatial Delayed Response Task, collapsed across spatial and verbal interference conditions. Error bars represent standard errors of the mean. *p=.004 for difference from nonpsychiatric controls.

Appendix H

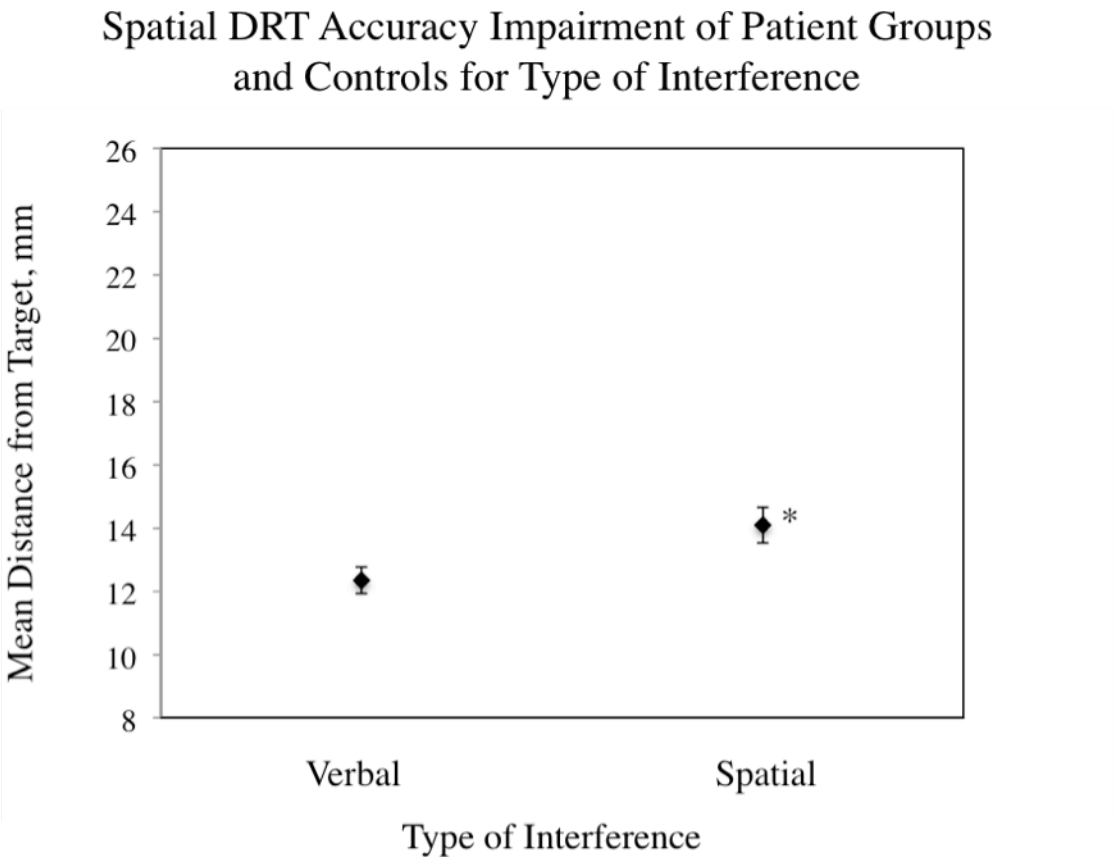

Figure 2. For patient groups and controls, average amount of impairment to accuracy on Delayed Response Task caused by different types of interference conditions. Error bars represent standard errors of the mean. * $\underline{p}<.0005$ for difference from Verbal interference condition.

Appendix I

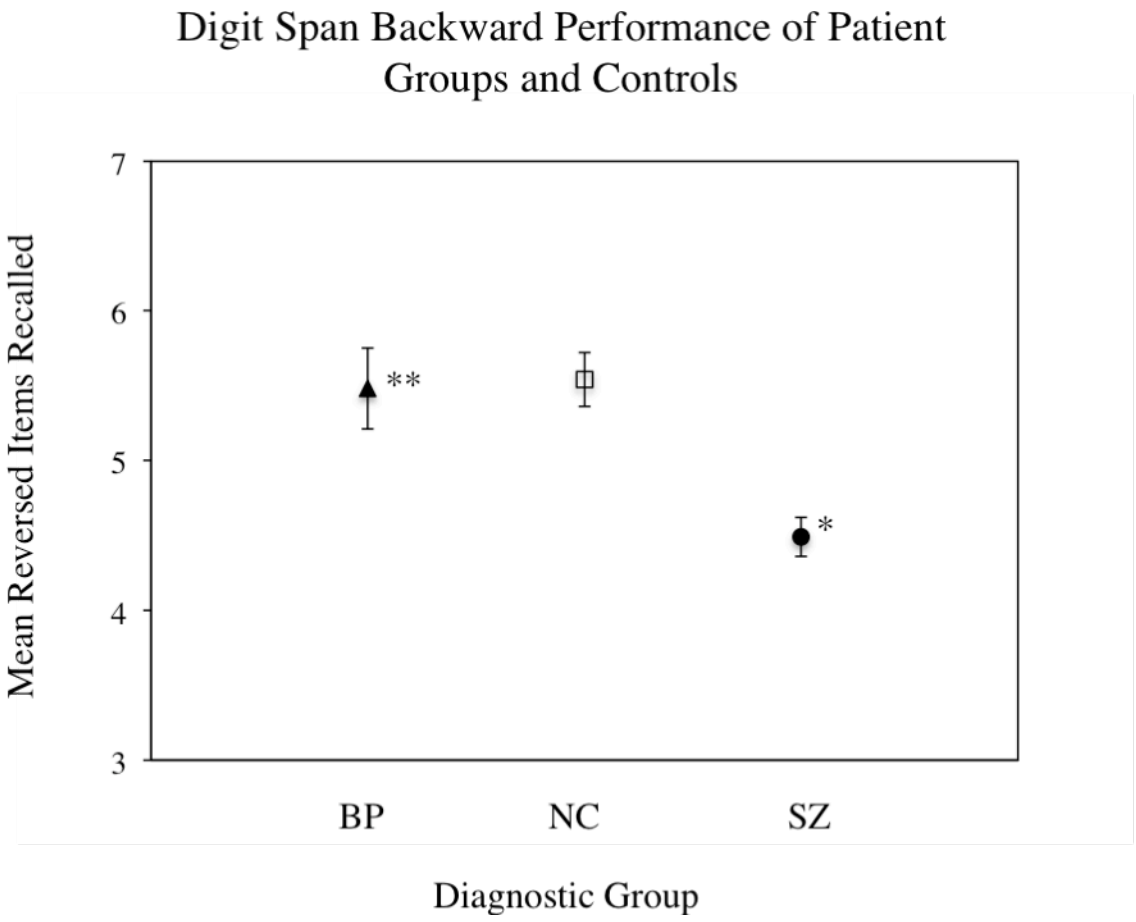

Figure 3. For patient groups and controls, average number of reversed items recalled on the Digit Span Backward. Error bars represent standard errors of the mean. * p<.0005 for difference from nonpsychiatric controls. **p<.001 for difference from schizophrenia patients.

Appendix J

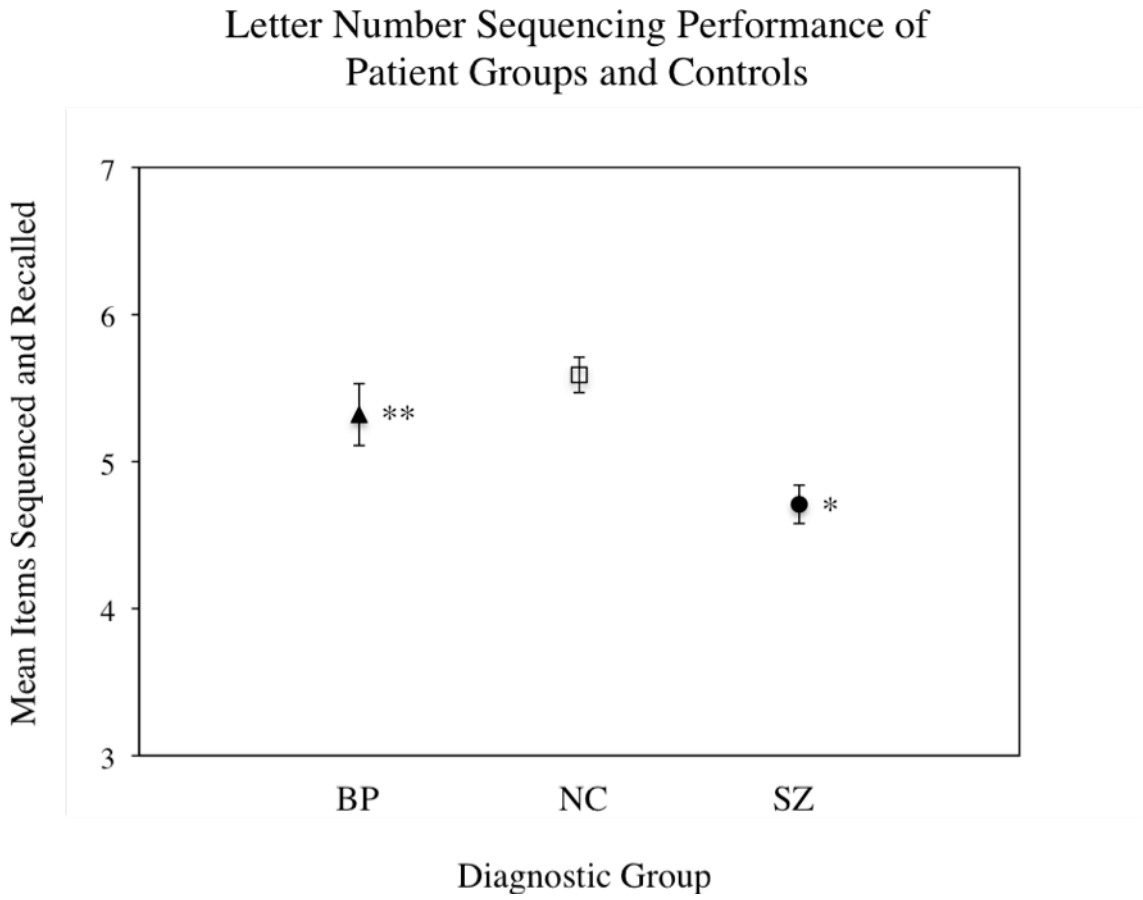

Figure 4. For patient groups and controls, average number of items sequenced and recalled on the Letter Number Sequencing Task. Error bars represent standard errors of the mean. * $p<.0005$ for difference from nonpsychiatric controls. ** $p<.007$ for difference from schizophrenia patients.

Appendix K

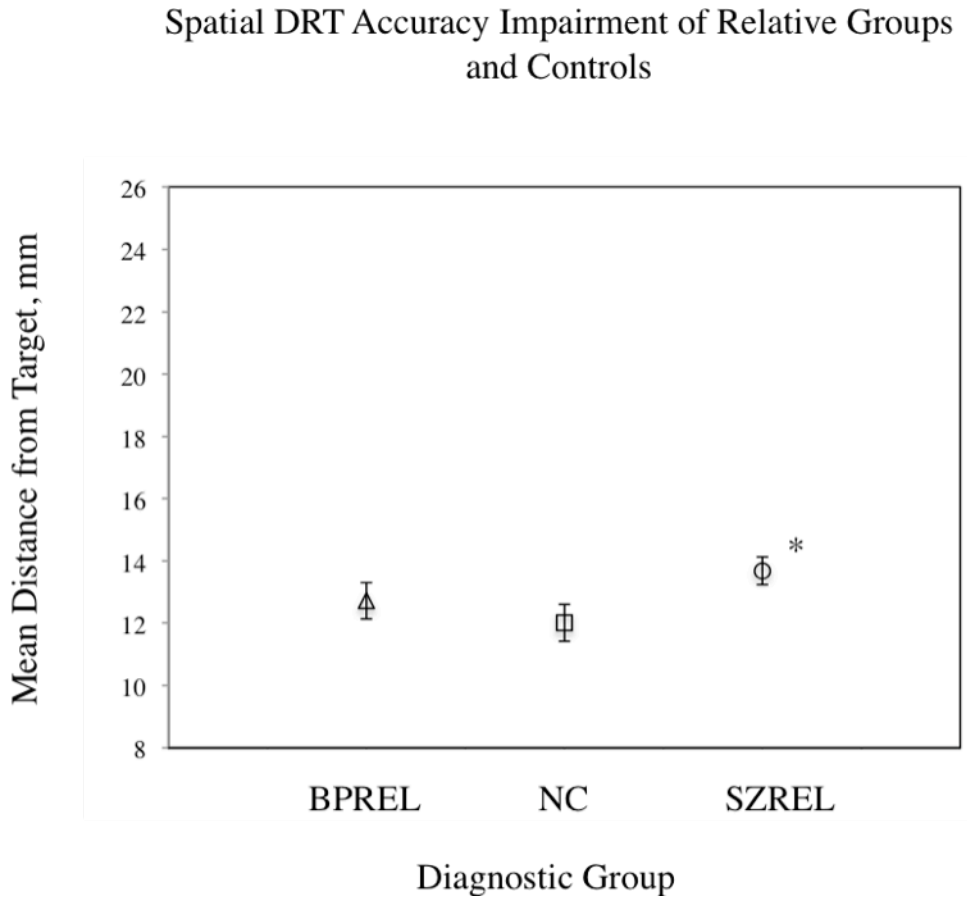

Figure 5. For relative groups and controls, average amount of impairment to accuracy on Delayed Response Task, collapsed across spatial and verbal interference conditions. Error bars represent standard errors of the mean. * p=.02 for difference from nonpsychiatric controls.

Appendix L

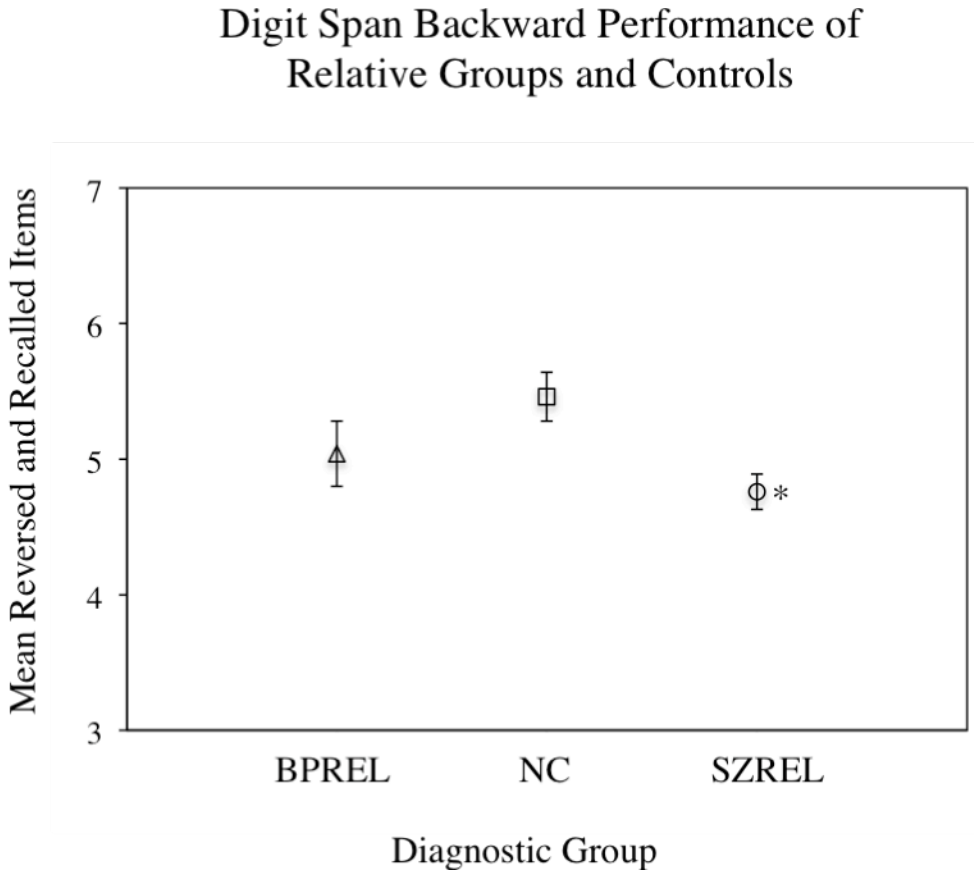

Figure 6. For relative groups and controls, average number of reversed items recalled on the Digit Span Backward. Error bars represent standard errors of the mean. * p=.002 for difference from nonpsychiatric controls.

Appendix M

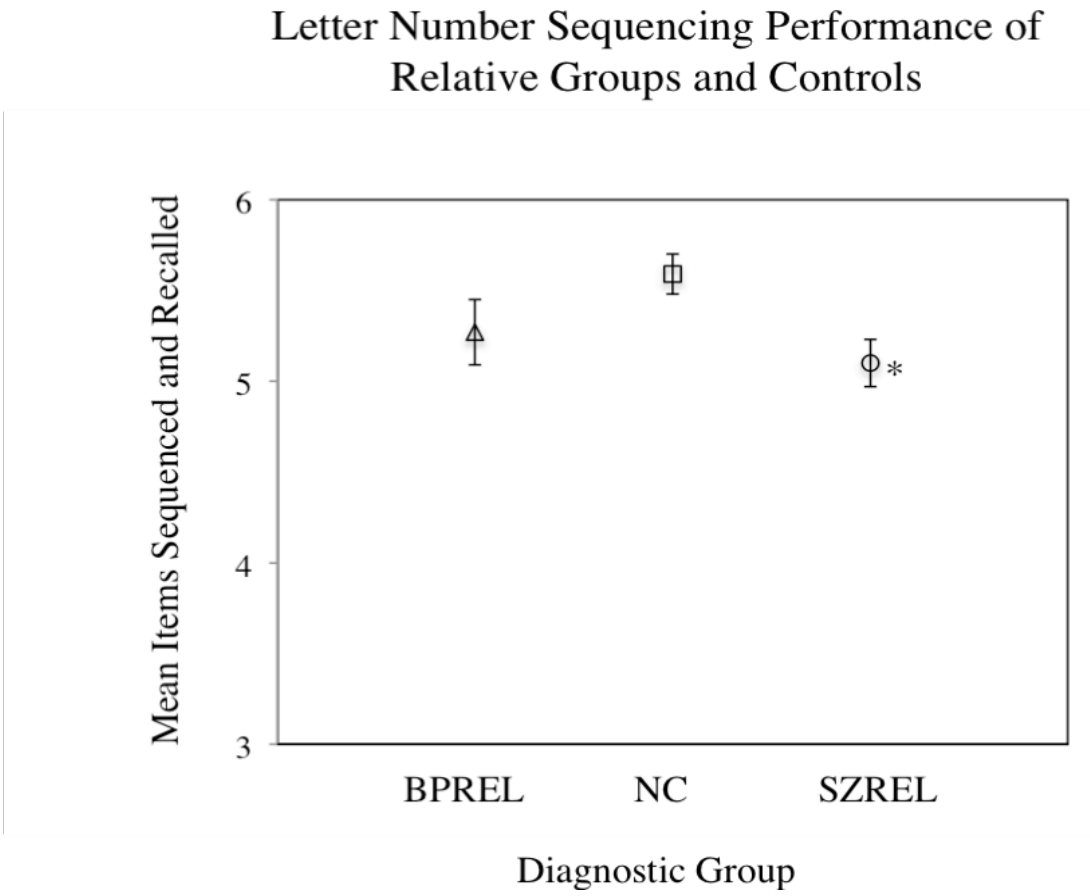

Figure 7. For relative groups and controls, average number of items sequenced and recalled on the Letter Number Sequencing Task. Error bars represent standard errors of the mean. * p=.006 for difference from nonpsychiatric controls.

Appendix N

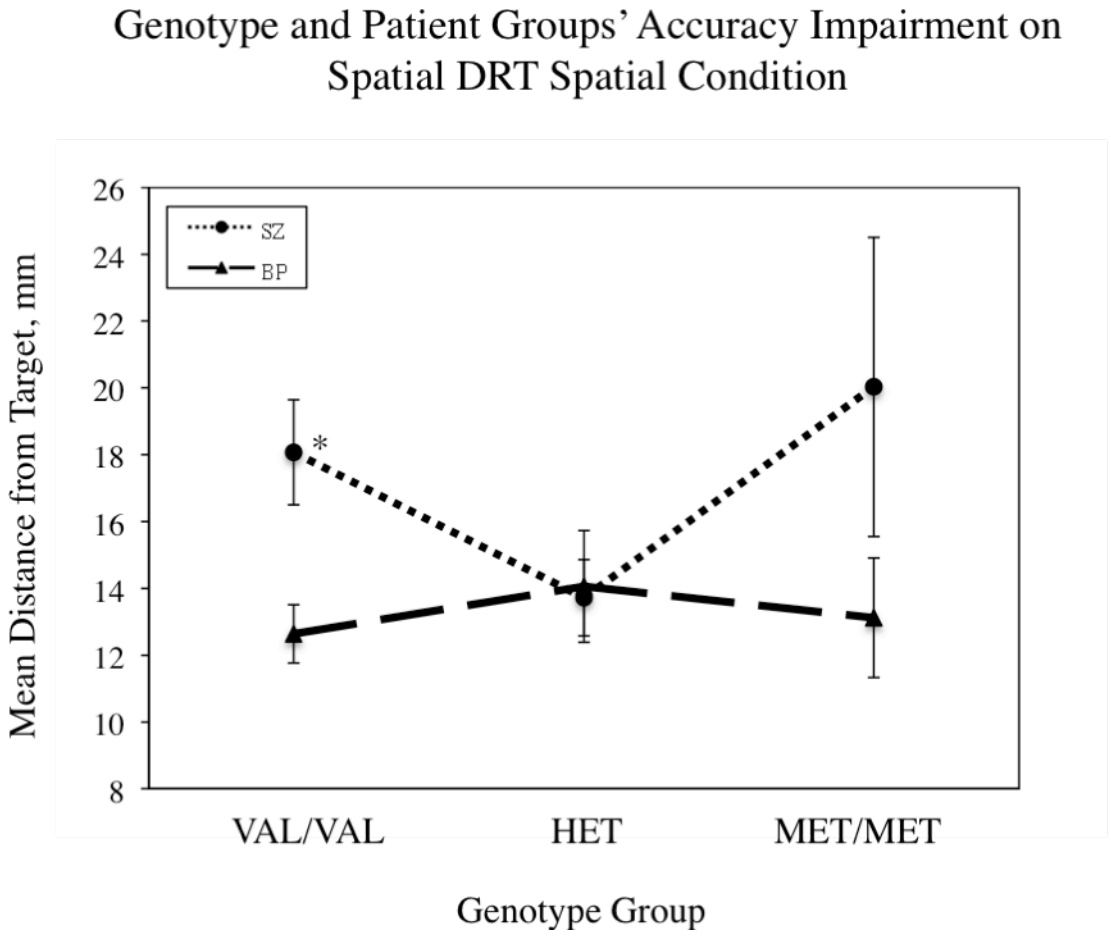

Figure 8. For all genotype and patient groups, average amount of impairment to accuracy on the Delayed Response Task caused by spatial interference. Error bars represent standard errors of the mean. * p=.03 for difference from bipolar disorder patients with Val/Val genotype.

Appendix O

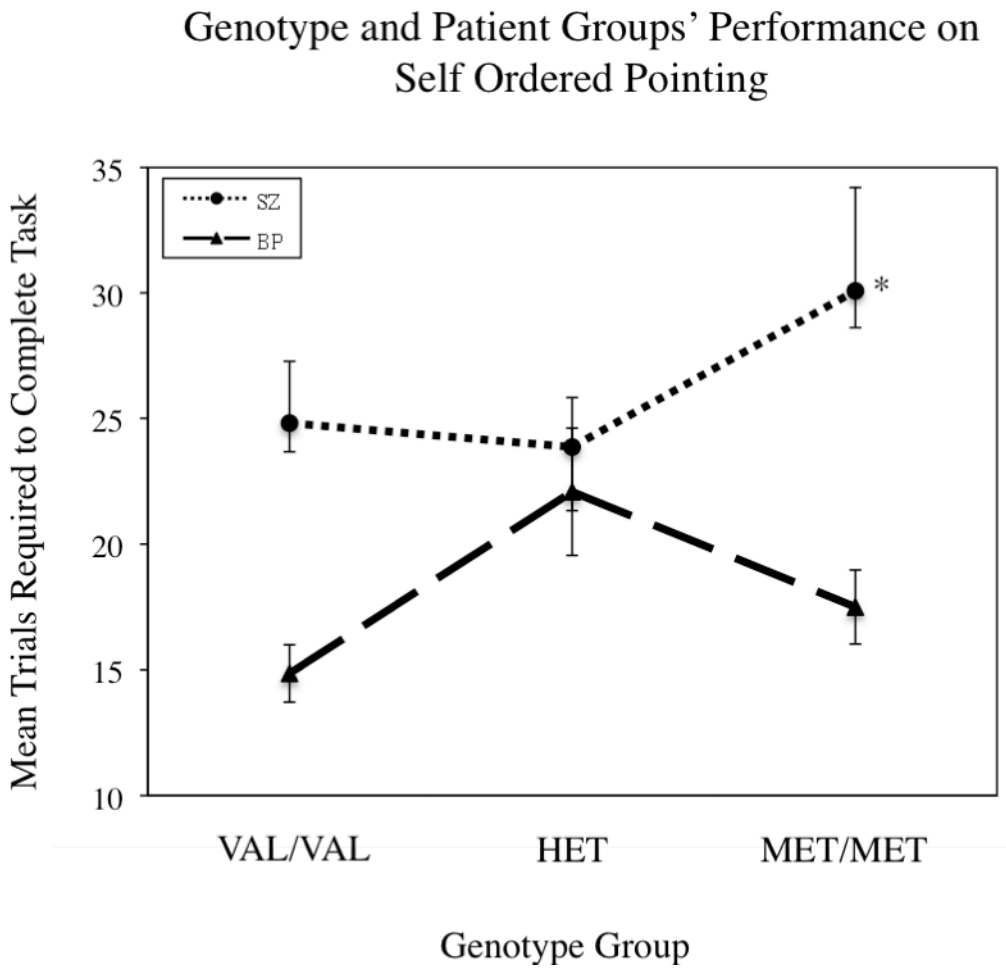

Figure 9. For all genotype and patient groups, average number of trials required to complete the Self Ordered Pointing Task. Error bars represent standard errors of the mean. * p=.001 for difference from bipolar disorder patients, collapsed across genotype groups.

Appendix P

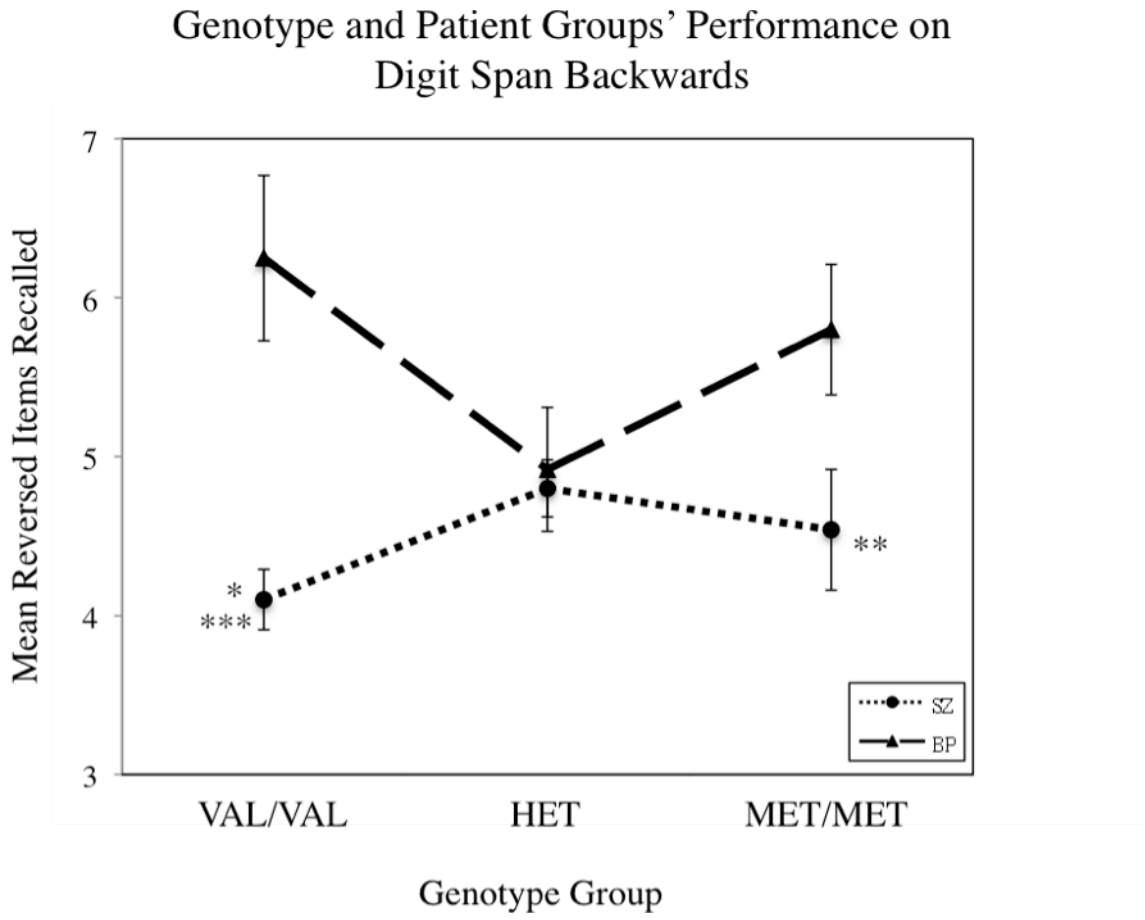

Figure 10. For all genotype and patient groups, average number of reversed items recalled on the Digit Span Backward. Error bars represent standard errors of the mean. * $\underline{p}$<.0005 for difference from Val homozygote bipolar disorder patients. ** $\underline{p}$=.04 for difference from Met homozygote bipolar disorder patients. *** $\underline{p}$=.08 for difference between schizophrenia patients with Heterozygote genotype.

Appendix Q

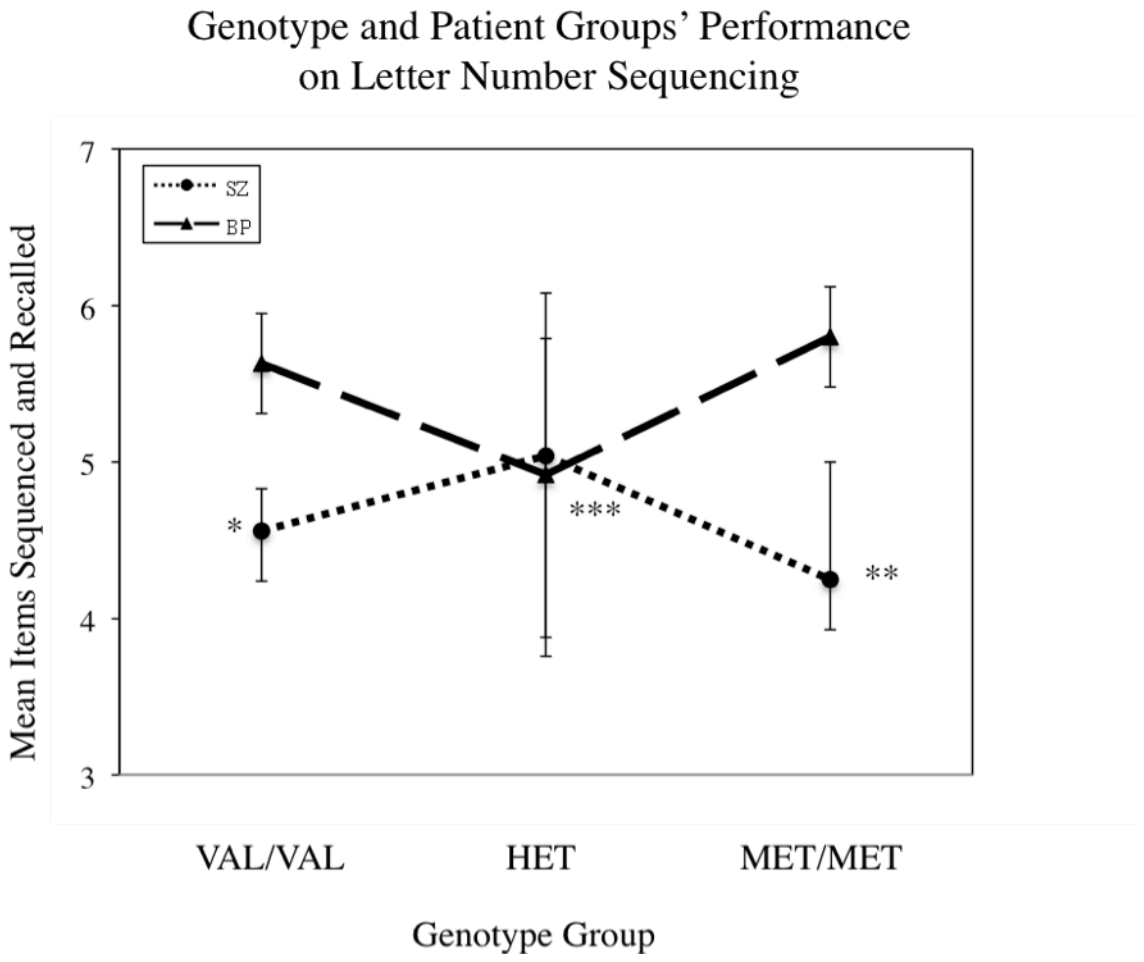

Figure 11. For all genotype and patient groups, average number of items sequenced and recalled on the Letter Number Sequencing Task. Error bars represent standard errors of the mean. * p=.03 for difference from Val homozygote bipolar disorder patients. ** p=.001 for difference from Met homozygote bipolar disorder patients. *** p=.02 for difference from schizophrenia patients with Met homozygote genotype.

Appendix R

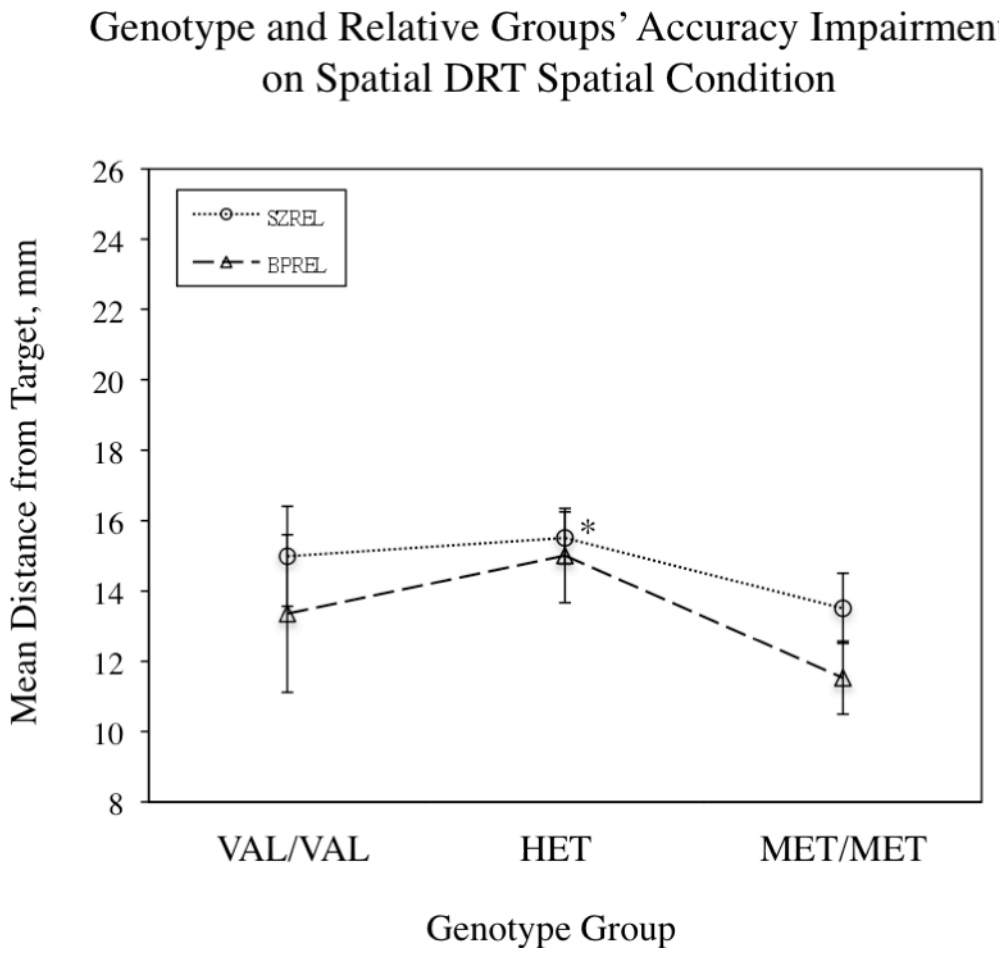

Figure 12. For all genotype and relative groups, average amount of impairment to accuracy on the Delayed Response Task caused by spatial interference. Error bars represent standard errors of the mean. * p=.02 for difference from Met homozygote genotype, collapsed across Diagnostic Groups.

Appendix S

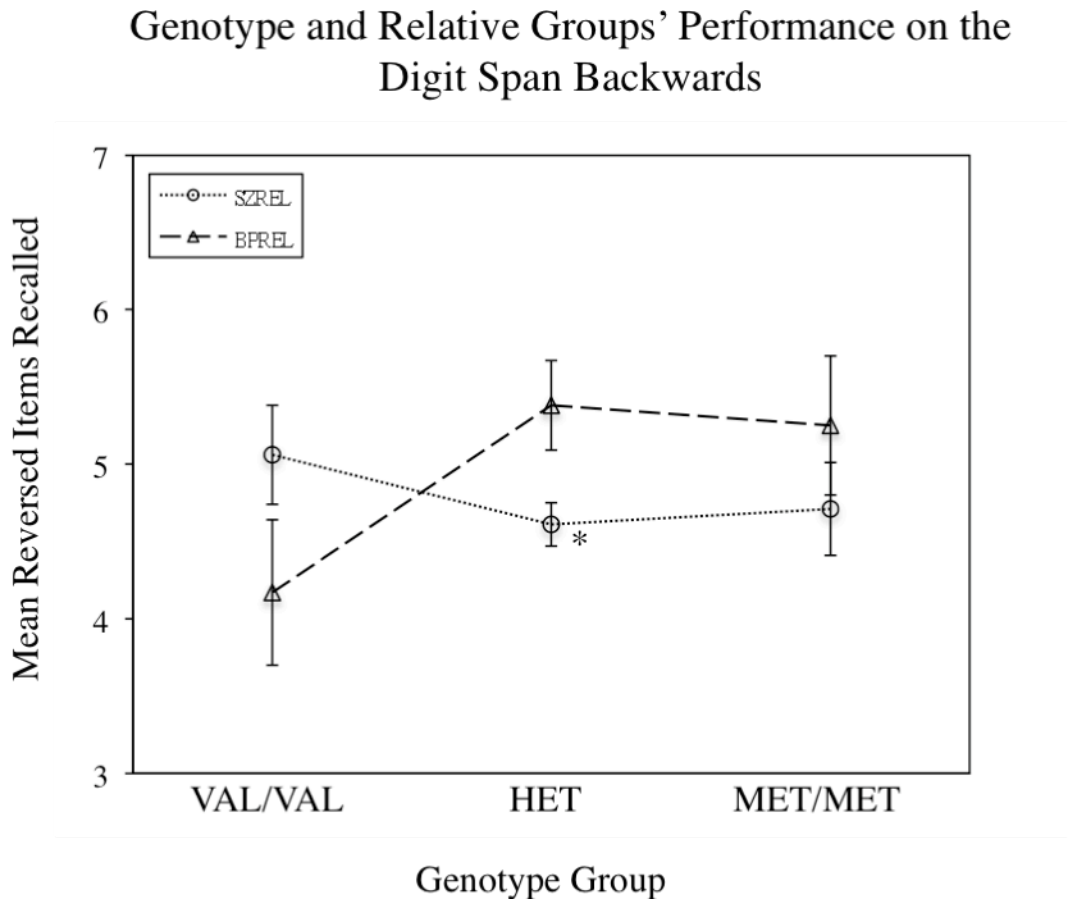

Figure 13. For all genotype and relative groups, average number of reversed items recalled on the Digit Span Backward. Error bars represent standard errors of the mean. * p=.01 for difference from relatives of bipolar disorder patients with Heterozygote genotype.

Appendix T

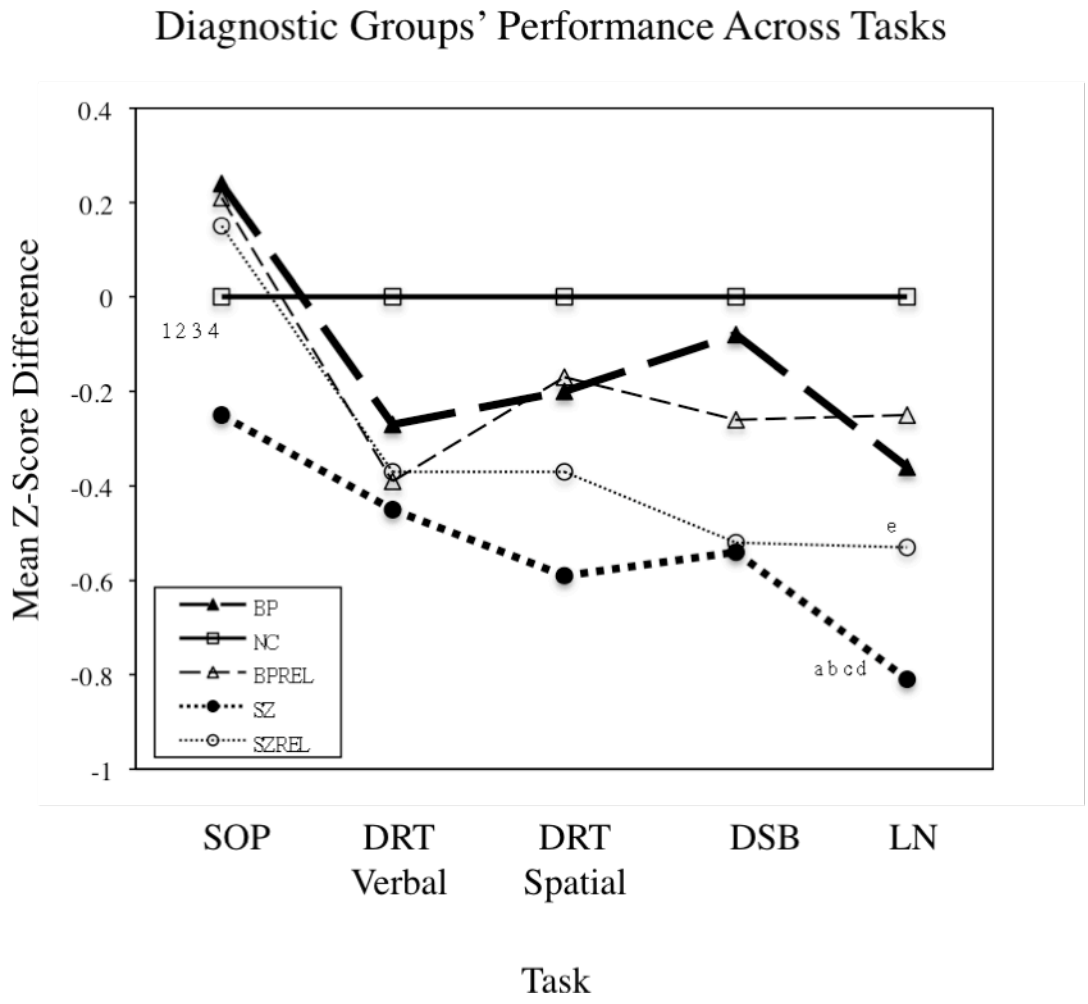

Figure 14. For all patient, relative, and nonpsychiatric control groups, the mean z-score difference from nonpsychiatric controls across tasks. a = p<.0005 for difference from nonpsychiatric controls. b = p=.002 for difference from bipolar disorder patients. c = p=.009 for difference from relatives of bipolar disorder patients. d = p=.057 for difference from relatives of schizophrenia patients. e = p=.02 for difference from nonpsychiatric controls. 1 = p<.0005 for difference from verbal interference condition of Spatial Delayed Response Task. 2 = p<.0005 for difference from spatial condition of Spatial Delayed Response Task. 3 = p<.0005 for difference from Digit Span Backward. 4 = p<.0005 for difference from Letter Number Sequencing.