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The neurocognitive impairment associated with comorbid schizophrenia and Ptsd

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THE NEUROCOGNITIVE IMPAIRMENT ASSOCIATED WITH
COMORBID SCHIZOPHRENIA AND PTSD

by

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A dissertation submitted in partial fulfillment
of the requirements for the

**Doctorate of Philosophy Degree in Psychology
Department of Psychology
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ABSTRACT

The Neurocognitive Impairment Associated with Comorbid Schizophrenia and PTSD

by

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Individuals with severe mental illness report a higher incidence of trauma and PTSD than the general population. A trauma history in individuals with schizophrenia has been associated with more severe psychiatric symptoms including positive symptoms, depression, suicidality, anxiety, somatization and dissociation (Beck & van der Kolk, 1987; Craine, Henson, Colliver & MacLean, 1988; Ross, Anderson & Clark, 1994; Darves-Bornoz, & Gaillard, 1995; Holowka, King, Saheb, Pukall & Brunett, 2003; Strauss et al., 2006).

The current study is among the first to examine the influence of comorbid schizophrenia and PTSD by performing comprehensive diagnostic, symptom and neurocognitive evaluations on four groups: normal controls ($n = 26$), a PTSD group ($n = 21$), a schizophrenia group ($n = 26$), and a group of individuals with schizophrenia and PTSD ($n = 21$).

Participants were administered the Structured Clinical Interview for DSM-IV-TR Diagnosis (SCID). Those who met diagnostic criteria were administered a battery of tests

designed to assess psychiatric symptoms (Schedule for the Assessment of Negative Symptoms, Schedule for the Assessment of Positive Symptoms, Brief Psychiatric Rating Scale, the Calgary Depression Rating Scale, and the Post-traumatic Stress Disorder Checklist-Civilian) and an extensive battery of neuropsychological tests in order to assess all major neurocognitive domains. It was hypothesized that the combined effects of schizophrenia and PTSD would produce greater neurocognitive impairment than either disorder when it occurred alone.

Results of neurocognitive tests indicated that the schizophrenia groups performed significantly worse than the Control and PTSD groups in all neurocognitive domains. No significant differences were present between the PTSD and Control group. While the differences were not significant between the comorbid group (SZP) and the schizophrenia only group (SZ), there were some domains in which the mean performance of the SZP group was different than the means of the SZ group. The SZP group performed approximately one standard deviation poorer than the SZ group on the Attention Domain. Conversely, the SZP group scored approximately one-half of a standard deviation better than the SZ group on the Executive Domain and the Visual Learning/Memory Domain. Results of this study do not support the idea that the presence of comorbid PTSD results in increased cognitive impairment in schizophrenia, more than what might be expected in schizophrenia alone. In fact, the presence of PTSD in individuals with schizophrenia may be associated with slightly better performance in many neurocognitive domains. Results of this study do, however, suggest some areas of neurocognitive function to further investigate, including Attention, Executive Function, and Visual Memory. In conclusion, while the presence of PTSD in individuals with schizophrenia is associated

with a different pattern of psychiatric symptoms, PTSD may not significantly impact neurocognitive function in a consistent manner, if at all.

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CHAPTER 1

INTRODUCTION

Traumatic events are no longer considered “outside the realm of normal experience” as once described in the DSM-III (APA, 1980). The definition of what constitutes a traumatic event has subsequently been revised and includes two components in the DSM-IV p. 424 (APA, 1994). The person must have been exposed to a “catastrophic event involving actual or threatened death or injury, or a threat to the physical integrity of him/herself or others and the person's response was marked by intense fear, helplessness, or horror”. This change was made in response to epidemiological studies indicating that a large number of people have survived a traumatic event. Current estimates suggest that more than half of the people in the United States are exposed to a traumatic event in their lifetime and a substantial portion of these individuals go on to develop post-traumatic stress disorder (Kessler et al., 1995). Prevalence rates may be substantially higher around the world than in the United States. For example, the rates of traumatic events and corresponding diagnoses of post-traumatic stress disorder (PTSD) in countries that have recently undergone political duress and civil disobedience ranges from the upper teens to almost 40 percent (de Jong et al., 2001). Additionally, considering that many traumatic events are not reported, the actual numbers may be much higher than those currently reported.

These statistics become especially alarming when one considers populations with severe mental illness, such as schizophrenia. Individuals with severe mental illnesses are at a greater risk for experiencing trauma, although they may be less likely than other people to report that they have been exposed to a traumatic event. Resnick, Bond and Mueser (2003) found that 38% of those with schizophrenia who had been traumatized had not discussed it with a counselor, 36% had never told a friend or family member, and 28% had told no one other than the researchers in their study. The presence of recent trauma (within the last year) was reported by 79% of mentally ill women (Cascardi, Mueser, DeGirolomo, & Murrin, 1996). Some of these individuals who are exposed to a traumatic event will later develop PTSD, and so the increased prevalence of traumatic events associated with schizophrenia coincides with a higher prevalence of PTSD in these individuals. The incidence of PTSD in individuals with severe mental illnesses is between 29% and 43% compared to an 8% prevalence rate in the general population (Mueser, Salyers, Rosenberg, Ford, Fox, & Carty, 2001).

There is also evidence to suggest that trauma history in people with schizophrenia is associated with deleterious effects including increased symptoms and poorer functional and treatment outcomes. In those without schizophrenia, Ross, Anderson and Clark (1994) found more positive symptoms of schizophrenia in those with a history of childhood abuse. Similarly, in individuals with schizophrenia, a history of physical or sexual abuse is related to more severe psychiatric symptoms including positive symptoms, depression, suicidality, anxiety, somatization and dissociation (Beck & van der Kolk, 1987; Craine et al., 1988; Holowka, King, Saheb, Pukall, & Brunet, 2003; Strauss et al., 2006). Trauma history has also been associated with hostile behavior,

substance abuse, and homelessness in those with schizophrenia (Goodman, Rosenberg, Mueser & Drake, 1997; Mueser, Goodman, Trumbetta, Rosenberg, Osher, Vidaver, Auciello, & Foy, 1998; Lysaker, Meyers, Evans, & Marks: 2001). Furthermore, it has been noted that psychiatric patients who have a history of abuse as children are more likely to attempt suicide, have more symptoms, receive more medication, have longer hospitalizations, and have an earlier first admission for psychiatric treatment (Mueser et al., 2002; Read & Ross, 2003).

To date, there have been few studies that have examined schizophrenia and PTSD comorbidity, despite a large body of evidence suggesting that both schizophrenia and PTSD are associated with underlying neurobiological dysfunction. The only study examining neurological function associated with a trauma history in individuals with schizophrenia found deficits in working memory and information processing (Lysaker, Meyer, Evans, & Marks, 2001). These results suggest that the presence of trauma may be associated with increased neurocognitive impairment, which would be expected to become more severe with diagnosis of PTSD. The underlying neurobiological disruption and the resultant deficiencies in neurocognitive function, or how these neurocognitive deficits contribute to the uniformly poor outcomes experienced by those with schizophrenia and comorbid PTSD is still unknown. This study utilized a four-group design and administered an extensive psychiatric and neuropsychological battery. Neurocognitive function assessment included Working Memory, Explicit Memory, Attention, Executive Function, Emotional Function and Motor Function, representing the neurological areas implicated in both schizophrenia and PTSD.

Results of the current study indicated that the presence of PTSD was associated with increased levels of positive symptoms as measured by the SAPS, decreased negative symptoms as measured by the SANS, increased levels of depression, overall psychiatric distress, and PTSD symptoms. This study hypothesized that the neurocognitive function associated with comorbid schizophrenia and PTSD would support a synergistic model where the impairment would be more than the sum of the deficits associated with each disorder alone, wherein those neurobiological systems that are compromised in schizophrenia are particularly susceptible to the neurotoxic cascade of stress hormones associated with PTSD, however this was not supported by the current study. The presence of PTSD may not have contributed to increased neurocognitive impairment because of the severity of the deficits associated with schizophrenia alone, meaning that the neurocognitive deficits associated with schizophrenia are so severe that the impact of stress resulting from trauma may not further impact function. In the particular neurocognitive domains, the Attention Domain may represent an interaction effect in that it was the only domain where the comorbid group exhibited slightly poorer performance. Similarly, in comparing the PTSD and Control group, there were no significant differences. Although not significant, the Visual Memory Domain appears to be influenced by PTSD and should be investigated further in PTSD and comorbid schizophrenia PTSD and schizophrenia.

The results of this study have a number of important implications. First, they can contribute to improved treatments and functional outcomes in individuals with comorbid schizophrenia and PTSD. Results of the study suggest that clinicians working with individuals with schizophrenia should evaluate their clients for a history of traumatic

events to better treat psychiatric symptoms resulting from PTSD. Second, results of this study suggest that the presence of PTSD does not contribute to additional neurocognitive deficits. However, there was an interaction effect for the Attention Domain indicating that the presence of comorbid PTSD may selectively impair performance on this domain. The results also provide a first step in understanding the complex neurobiological dysfunction present in this comorbid group, and thus provide direction for future studies using different experimental methodologies (e.g., neuroimaging).

CHAPTER 2

LITERATURE REVIEW

For individuals with schizophrenia and other severe mental illnesses the rates of exposure to traumatic events range from 87% to 97% (Jacobsen, 1989; Lipschitz et al., 1996; Hutchings & Dutton, 1993; Goodman, Rosenberg, Mueser & Drake, 1997; Goodman et al., 1995). Trauma history in individuals with schizophrenia is associated with a worsening of symptoms, higher rates of substance abuse, greater risk of homelessness, and increased hospitalization (Goodman et al., 2001). Given the high prevalence of trauma in those with schizophrenia, combined with the increased symptoms, it is somewhat surprising that few studies have attempted to characterize the emotional, interpersonal, social and cognitive function in those individuals with comorbid schizophrenia and post-traumatic stress disorder (PTSD). To address this important deficiency in the research literature, the current study will investigate cognitive function in individuals with comorbid PTSD and schizophrenia. In the following sections, literature is reviewed that is relevant to schizophrenia and PTSD, with an emphasis on cognitive and neurological abnormalities, in order to provide a background for forming hypotheses regarding the neurocognitive dysfunction resulting from comorbid schizophrenia and PTSD. Ultimately, results of this study can inform mental health professionals working with individuals with schizophrenia of the importance of detection and treatment of trauma with the hopes of minimizing the sequelae of trauma.

Schizophrenia

Schizophrenia is one of the most severe and chronic mental illnesses and the presentation and prevalence of the disorder is consistent throughout the world.

Schizophrenia has been documented as early as two millenniums before Christ, in Egypt, and is present across the world. The lifetime prevalence rate of schizophrenia ranges from 1.4 - 4.6 per 1000 (Jablensky, 2003). Another review of the lifetime prevalence of schizophrenia found a mean rate of 4% (Saha, Chant, Welham, and McGrath, 2005). These prevalence rates are much higher than the .5% and 1% prevalence documented in the DSM-IV (APA, 1994) or the National Institute of Mental Health (NIMH). However, based on the more commonly accepted prevalence rate of 1.1%, 2.2 million Americans would be affected by schizophrenia (Regier, Narrow, Rae et al., 1993).

Schizophrenia is a lifetime disorder with age of onset in the late teens or early 20's. Because of the severity and pervasiveness of the deficits associated with schizophrenia, many individuals are unable to maintain employment or live independently. Schizophrenia is one of the top ten causes of disability in the United States and costs approximately \$65 billion a year (Wyatt, 1996). Without support systems and the ability to live independently, many people with schizophrenia end up homeless. In fact, individuals with schizophrenia make up one-third of the homeless population. Individuals with schizophrenia have a shorter life span than the general public because of a 10% incidence of suicide, comorbid substance use disorders (in particular nicotine dependence), poor nutrition, and inadequate living conditions. These statistics become especially troubling considering that many of these adverse consequences could be mitigated with proper treatment. The World Health Organization

reported that 80% of individuals with schizophrenia could be free of relapses each year with proper treatment (World Health Organization, 2003).

Because schizophrenia is a brain disorder, people with schizophrenia exhibit problems in a broad range of cognitive and emotional functions. The most characteristic symptoms include hallucinations and delusions. Individuals with schizophrenia also exhibit disorganized speech, disorganized behavior, flattening of affect, and loss of the ability to experience pleasure (anhedonia). Individuals with schizophrenia may also show impoverishment of mental abilities including impairments in language, memory, attention, abstraction, motor function and emotional processing. Associated neurobiological abnormalities include abnormal brain activity documented in EEG and imaging scans of the brain, eye tracking impairment, ventricular enlargement, brain asymmetry, decreased temporal lobe and hippocampal size, increased size of the basal ganglia, decreased brain size and abnormal blood flow in the prefrontal cortex (Liddle & Pantelis, 2003). These neurocognitive deficits and neurobiological abnormalities have been found in individuals who are experiencing their first episode of schizophrenia and have never been treated, as well as, in patients with a chronic disease course. Similar deficits that are of a less severe nature have also been identified in unaffected first-degree relatives of those with schizophrenia. A more in depth discussion of these neurocognitive findings and their corresponding neurophysiological abnormalities will be provided later. Neurocognitive deficits are core features of schizophrenia, and are not simply the result of other factors commonly associated with the disorder, such as medication effects, symptom severity, length of institutionalization, limited educational opportunities, etc.

Etiology

The search for causative factors in the development of schizophrenia has focused on both environmental and genetic influences. The diathesis stress model is the most widely accepted model of schizophrenia. In this model, genetic vulnerability combined with environmental influences results in abnormal brain development and expression of schizophrenia. Investigation of environmental influences has predominantly been limited to perinatal factors such as birth complications, exposure to influenza in utero, etc. More recently, environmental influences during early childhood have been examined with an emergence of research documenting that early life stressors also alter brain development. Thus, it is clear that both genetic and environmental factors contribute to the onset of schizophrenia and the most consistent findings are reviewed in the following sections.

Family, twin and adoption studies provide the most conclusive evidence for a genetic component to schizophrenia. Most convincing are the differences in concordance rates for schizophrenia between monozygotic twins (46%) and dizygotic twins (14%) (Riley, Asherson, & McGuffin, 2003). Additionally, relatives of individuals with schizophrenia are much more likely to develop schizophrenia than the general population. For example, a sibling of an individual with schizophrenia has a 10.1% lifetime expectancy rate for the development of schizophrenia (Riley, Asherson, & McGuffin, 2003) in comparison to 1.1% for the general population. Additional support for the genetic influence in schizophrenia is provided by studies reporting that many unaffected first-degree relatives of individuals with schizophrenia will exhibit similar symptoms and neurocognitive deficits as those observed in schizophrenia, but to a lesser degree (Sponheim, Steele, & McGuire, 2004; Conklin, Curtis, Calkins, & Iacono, 2005; Chen et

al., 1998). Subsequently there is strong support from twin and family studies to implicate a genetic mechanism involved in the expression of schizophrenia.

Despite the strong evidence for the genetic influence provided by twin and family studies, there is not a single gene identified in schizophrenia. Thus far, genetic studies have documented abnormalities in many different genes. This line of research is yielding a remarkable number of genetic influences or separate gene mutations. Specifically, research has documented a specific mutation in the WCLI gene that is responsible for catatonic schizophrenia in one family (Lesch, 2001). Another study suggested that the HOPA gene may also play a role in the development of schizophrenia consisting primarily of positive symptoms. This gene is x-linked and so 1 in 30 men with this gene will have schizophrenia (Philibert, Andreasen, & Woods, 2004). Other research has documented abnormalities in the Dysbindin (Schwab et al., 2003), Neuregulin (Stefansson et al., 2002), COMT (Egan et al., 2001), and G72 genes (Lin et al., 1995). A particularly relevant genetic finding is the glutamate mutation on the SNP4 section of the GRM3 gene (Egan & Weinberger, 2004). This mutation is related to the neurocognitive impairments associated with schizophrenia. This section is only a brief review of the literature on the genetic markers of schizophrenia. These findings and others suggest that schizophrenia is genetically complex, (i.e., it is caused by multiple genes located on multiple chromosomes).

It is commonly believed that schizophrenia is a neurodevelopmental disorder. One of the most popular neurodevelopmental conceptualizations of schizophrenia is Crow's hypothesis (1990). Crow suggested that there is a genetically determined neurodevelopmental anomaly that impairs cerebral asymmetry. Because brain

asymmetry is not completed until the end of adolescence, this anomaly in brain asymmetry can go relatively undetected until this point in development. The end of adolescence is around the same time as the typical age of onset in schizophrenia. Others have also suggested that schizophrenia is a neurodevelopmental disorder linked to the abnormal development of critical brain regions. For example, Weinberger (1987) suggested that schizophrenia results from disturbed brain development during the pre or perinatal period. Together, these studies provide strong support for a schizophrenia genotype that is complexly inherited and may exert its effects by causing abnormal cerebral development.

According to the diathesis-stress model, environmental influences are also important in the etiology and expression of schizophrenia. Environmental stressors studied as risk factors for schizophrenia have included in utero stressors, birth complications and even the season or place of birth. In all cases, these risk factors are thought to cause early damage to the developing brain which, when combined with genetic predisposition, causes the expression of schizophrenia. Schizophrenia rates are higher in those infants who were exposed to infectious agents prenatally (Watson et al., 1984; Torrey et al., 1988) or viruses like influenza (Mednick et al., 1988; McGrath, 1994). Similarly, environmental stressors like famines during pre-natal development are correlated with an increased incidence of schizophrenia (Susser et al., 1996). Obstetric complications may also pose a risk factor for the development of schizophrenia, as obstetric hazards are associated with increased risk of brain injury. In particular, infants born prior to 32 weeks gestation have increased ventricular volume, corpus callosum abnormalities, smaller whole brain volumes, and smaller hippocampi similar to the

neurological findings seen with individuals who have schizophrenia (Nosarti et al., 2001). In males with schizophrenia, low birth weight is correlated with greater cognitive deficits (Rifkin et al., 1994). Somewhat surprisingly, one of the most consistent findings in regards to environmental influence is the season of birth. Those born in the late winter and spring are more likely to develop schizophrenia (Torrey et al., 1997). Being born or raised in the city is also associated with an increased risk of developing schizophrenia (Lewis et al., 1992; Takei et al., 1992), possibly due to increased exposure to environmental toxins. Thus, there is strong support for perinatal influences as risk factors for the development of schizophrenia.

Although the bulk of the research on environmental influences in schizophrenia has focused on perinatal factors, more recent research has suggested that early childhood experiences are also very important. The Finnish adoption study by Tienari (1991) provided compelling support for the importance of childhood experiences in the development of schizophrenia. In this study, adopted children of parents with schizophrenia had significantly different rates of schizophrenia when raised by “healthy” families (4%) as opposed to children raised by “disturbed” adoptive families (34%). It is also believed that other measures of family function are important in predicting schizophrenia. Variables such as parental hostility (Rodnick, Goldstein, Lewis, & Doane, 1984) or high expressed emotion have been associated with increased rates of schizophrenia and higher rates of relapse (Goldstein, 1985; Vaughn & Leff, 1976, 1981). Vaughn and Leff defined expressed emotion as high levels of intrusiveness and high levels of criticism. Also, criticism from family members has been correlated with increases in the patient’s unusual thinking (Hooley & Hiller, 1998). In fact, stressful

events are very common before the onset of schizophrenia (Brown & Birley, 1968; Day et al., 1987; Ventura, Nuechterlein, Lukoff & Hardisty, 1989). More recently, even stressors such as poverty have been implicated in development of schizophrenia (Cohen, 1993; Saraceno and Barbui, 1997), which has led to active efforts to identify life stressors that are substantive predictors of schizophrenia onset. One such stressor, which will be extensively reviewed later, is the experience of trauma. Eighty-seven percent of individuals with severe mental illnesses like schizophrenia have experienced at least one traumatic event (Goodman et al., 2001). Also, a trauma history has been correlated with more severe symptoms of schizophrenia and other deleterious effects (Beck & van der Kolk, 1987; Craine et al., 1988; Ross, Anderson & Clark, 1994). Therefore, research has shown that schizophrenia is a disorder that may be caused by genetic and environmental factors that combine to produce abnormal neurodevelopment, which is expressed as schizophrenia.

Neurological Function in Schizophrenia

Although schizophrenia has long been considered a disorder of the brain, neurocognitive testing and neuroimaging techniques have provided unequivocal evidence of structural and neurophysiological abnormalities. Despite the extensive amount of research regarding numerous neurophysiological deficits associated with schizophrenia, findings with regard to neurophysiological deficits are not as consistent across individuals as the neurocognitive deficits (Liddle and Pantelis, 2003). A meta-analysis evaluating brain volume in schizophrenia indicated that there is a 2% reduction in whole brain volume (Ward et al., 1996; Wright et al., 2000), which may be primarily gray matter in the heteromodal association cortex (Schlaepfer et al., 1994). Another

frequently discussed neurological difference in schizophrenia is a lack of normal brain asymmetry. Individuals without schizophrenia are more likely to have left hemisphere dominance, whereas individuals with schizophrenia lack this normal asymmetry (Maher & Deldin, 2001). In the following sections the brain structures that are most consistently implicated in schizophrenia will be reviewed including the temporal lobe, frontal lobe, and subcortical structures. Sections will include findings from both structural and functional neuroimaging techniques.

Temporal Lobe. The temporal lobes have been implicated in some of the key schizophrenia symptoms such as hallucinations, negative symptoms and disorganized speech (Vignall, Maillard, McGonigal, & Chauvel, 2007; Weinstein, Woodward & Ngan, 2007; Thomas et al., 2005). Additionally, the superior temporal gyrus has a role in the auditory perception and expression of language and therefore may be related to auditory hallucinations and formal thought disorder (Liddle & Pantelis, 2003; Petty et al., 1995). The most consistent neurophysiological finding in schizophrenia is enlargement of the ventricles (Liddle & Pantelis, 2003) and in particular the temporal horns of the lateral ventricles and the third ventricle (Johnstone et al., 1976; Hopkins & Lewis, 2000). Examination of the lateral temporal lobe also provides support for the deficits related to thought disorder as the volume in the superior temporal gyrus was inversely correlated to the severity of thought disorder (Shenton et al., 1992). There have also been abnormalities detected in the size of the temporal lobe in individuals with schizophrenia (Southard, 1915). The superior temporal gyrus and the planum temporale have reduced volume which is evident in the first episode of schizophrenia suggesting that it is not the result of disease chronicity, medication effects, or other related disease variables

(Hirayasu et al., 1998). Results of a meta-analysis on the size of the medial temporal structures (hippocampus and amygdala) revealed a bilateral reduction of 4% (Nelson, Saykin, Flashman, & Riordan, 1998). Bilateral reduction may not be present until later in the disease, while the left-hippocampal volume reduction is present at the first-episode of schizophrenia (Velakoulis et al., 1999). Overall, structural neuroimaging studies have detected abnormalities or decreased volume in superior temporal cortex and hippocampal regions in individuals with schizophrenia, which appear to result from both genetic and environmental influences.

Post mortem studies have also indicated changes in the cytoarchitecture of the hippocampus suggestive of abnormal cortical migration (Jakob & Beckmann, 1986, 1994). Some of the cellular or molecular findings include smaller neurons in the hippocampal region of individuals with schizophrenia compared to those of controls (Arnold, 2000), poorly formed and disorganized clusters of neurons in the entorhinal cortex, abnormal expression of MAP2 gene, abnormal expression of mRNA products, and inappropriate glutamatergic and catecholaminergic innervation of the entorhinal cortex (Arnold, 2000).

Functional neuroimaging and ERP studies further document hippocampal dysfunction in schizophrenia and have also demonstrated associations between this dysfunction and some of the core symptoms of schizophrenia. Functional studies have implicated the medial temporal structures in the positive symptoms of schizophrenia (Liddle & Pantelis, 2003). A decrease in the P300 wave on ERP in individuals with schizophrenia is correlated with thought disorder (Roth, Pfefferbaum, Kelly, Berger, & Kopell, 1981). Heckers et al. (1998) found reduced hippocampal activation using PET

scans in individuals with schizophrenia during episodic memory tasks. However, other studies have not found significant correlations between memory performance and hippocampal size or function (Busatto et al., 1994). Despite some contradictory findings the functional studies of the temporal lobe provides additional evidence for hippocampal dysfunction in schizophrenia.

Limbic System. Various components of the limbic system have also been extensively investigated in schizophrenia, including the hippocampus, which was discussed earlier, as well as the anterior cingulate and the amygdala. Limbic system abnormalities are thought to contribute to some of the core features of schizophrenia, including emotional dysregulation and blunting, attentional deficits, and impaired response inhibition. For example, the anterior cingulate is associated with attentional processes and response inhibition. Some structural neuroimaging studies have documented decreased volume of the cingulate cortex in individuals with schizophrenia (Goldstein et al., 1999). Decreased volume and lack of normal asymmetry of the anterior cingulate has also been found in individuals with childhood onset schizophrenia (Marquardt et al., 2005). Furthermore, there is evidence to suggest that there is a reduction in the nonpyramidal neurons in layers II-VI of the anterior cingulate in individuals with schizophrenia (Todtenkopf, Vincent, & Benes, 2005). Other studies have found no structural differences in the anterior cingulate (Hirayasu et al., 1999), however the overall findings with regard to structural changes of the anterior cingulate suggest that individuals with schizophrenia have decreased volume in this region.

It would also be expected that functional studies of the anterior cingulate would reveal some abnormalities in individuals with schizophrenia. Similar to the structural

studies, functional studies are somewhat inconsistent. A meta-analysis documented consistent increases in the activation of the anterior cingulate in individuals with schizophrenia (Glahn et al., 2005). Some single experimental studies have found decreases in the activation of the anterior cingulate. For example, Carter et al. (1997) found decreased activation of the anterior cingulate during the Stroop task in individuals with schizophrenia. Deficiencies of the anterior cingulate have also been correlated with the disorganized symptoms of schizophrenia (Liddle et al., 1992). So while the findings regarding the anterior cingulate function are not conclusive, the research indicates that there is an overall trend towards increased activation in individuals with schizophrenia.

The amygdala is another component of the limbic system and dysfunction in this structure would be associated with emotional processing deficits. MRI studies have shown reduced volume and reduced gray matter density of the amygdala (Gur et al., 2000; Breier et al., 1992). Niu et al. (2004) found that males had bilateral reduction, while females had significantly smaller right amygdala. Additionally, there was a significant trend for the left amygdala to be smaller than the right for males with schizophrenia. So, while the majority of studies evaluating structural changes of brain regions evaluate the limbic system structures combined, ones that have specifically looked at the structure of the amygdala have documented decreased volume.

In conjunction with the structural deficits of the amygdala in schizophrenia, some functional abnormalities have also been identified. Schneider et al. (1998) found less activation of the amygdala in patients with schizophrenia using sad emotional prompts. Phillips et al. (1999) found that individuals with schizophrenia were less accurate and had less activation when identifying facial expressions than controls. Phillips et al. also

found that there was a difference in activation and accuracy of identifying facial expression based on the subtype of schizophrenia; individuals diagnosed with paranoid schizophrenia were more similar to controls than those people with other types of schizophrenia. Taylor, Liberzon, Decker, and Koeppel (2002) reported that individuals with schizophrenia did not exhibit activation of the amygdala in response to aversive stimuli. Thus, results of both structural and functional neuroimaging studies suggest impairment of the amygdala in schizophrenia.

Frontal Lobes. The frontal lobes are one of the primary brain structures implicated in the pathogenesis of schizophrenia. Functions of the frontal lobe include deficits in motivation, problem solving, abstraction, and decision-making. The localization of these abilities to the frontal lobe was primarily accomplished through individuals who had sustained damage to the prefrontal cortex (e.g., Shamay-Tsoory, Aharonj-Peretz, Levkovitz, 2007; Maher & Deldin, 2001). This literature has been linked to the deficits associated with schizophrenia. In individuals with schizophrenia, structural MRI studies have shown decreased volume of the frontal lobe (Andreasen et al., 1994, Breier et al., 1992, Nopoulos et al., 1995). Volumetric analyses indicate that the majority of the reduction is the result of grey matter loss in the dorsolateral and dorsomedial prefrontal cortex (Goldstein et al., 1999). The deficits in prefrontal volume may be caused by abnormalities in the composition or number of neurons (Liddle & Pantelis, 2003). The frontal lobe abnormalities are also found early in the progression of the disease (i.e., in those experiencing their first episode of the disorder that has never been medically treated) and are therefore interpreted by some as a central component in schizophrenia.

It is generally believed that the frontal lobe abnormalities seen in schizophrenia reflect a decrease in activity and correspondingly, functional neuroimaging studies have demonstrated this hypoactivity in the frontal lobe. Both PET and fMRI studies indicate that individuals with schizophrenia demonstrate hypoactivity in the prefrontal cortex while performing traditional tests of executive function, such as the Tower of London and Wisconsin Card Sorting Test (Andreasen et al., 1992; Kawasaki et al., 1993; Weinberger & Berman, 1996). In line with the idea that the pattern of activation is impaired in individuals with schizophrenia, Meyer-Lindenberg et al. (2001) found that controls exhibited dorsolateral prefrontal and anterior cingulate activity during working memory tasks, while all of the individuals with schizophrenia had inferotemporal, hippocampal and cerebellar activation during the same tasks. These findings could be interpreted to mean that as a result of prefrontal cortex dysfunction, individuals with schizophrenia recruit other brain structures to perform these tasks, which results in inefficient performance and neurocognitive deficits. Furthermore, fMRI studies of the frontal lobes have also suggested abnormal dopamine function in individuals with schizophrenia during working memory tasks (Meyer-Lindenberg, Poline, Kohn et al., 2001). The hypofrontality indicated by functional imaging studies may not be present through all phases of the illness and appears to be associated with specific symptoms of the disorder (Liddle, 1996). Decreased activity in the frontal lobes may be preferentially related to the negative symptoms in schizophrenia. Hypoactivity in the prefrontal cortex has also been associated with psychomotor poverty syndrome in schizophrenia (Liddle, 1996). ERP results have, however, linked frontal abnormalities to both the positive and negative symptoms of schizophrenia (Pritchard, 1986; van den Bosch et al., 1988). In conclusion,

neuroimaging techniques provide strong evidence for both structural and functional abnormalities in the frontal lobes, and particularly the dorsolateral and dorsomedial prefrontal cortices.

Basal Ganglia. The basal ganglia have also been of interest in schizophrenia research because of the high prevalence of movement disorders in this population. Among other things, the basal ganglia are responsible for controlling motor movements and smoothing fine motor behavior. The basal ganglia are made up of at least five subcortical nuclei including the putamen and globus pallidus (which are collectively called the lentiform nucleus), caudate nucleus, nucleus accumbens, septi, and olfactory tubercle. Damage to these structures can result in both hypokinetic movement disturbances, such as those observed in Parkinson's disease, as well as hyperkinetic movement disturbances, such as those present in Huntington's Chorea. Both hypokinetic and hyperkinetic movement disorders are present in those with schizophrenia, some resulting from treatment with antipsychotic medications, and others that are present prior to the onset of the disorder.

Structural neuroimaging studies have implicated a number of basal ganglia structures involved in schizophrenia. And, while some behavioral studies have documented clear neuromotor and movement disorders in children who later go on to develop schizophrenia (Schiffman, Walker, Ekstrom, Schulsinger, Sorensen, & Mednick, 2004; Walker, Savoie, & Davis, 1994; Walker, Lewis, Loewy, & Palyo, 1999), neuroimaging studies suggest that movement disorders may primarily result from the medication used to treat schizophrenia. McCreadie, Thara, Padmavati, Srinivasan, and Jaipurkar (2002) found volumetric differences of 11% in the left lentiform nucleus in

those individuals with schizophrenia that also exhibited movement disorders. Gunduz et al. (2002) did not find any difference in the volume of the basal ganglia structures in individuals with their first episode of psychosis. Gunduz et al. also did not find any age related differences and suggested that the volumetric differences seen in individuals with schizophrenia may be related to illness progression or use of antipsychotic medications. In fact, studies have shown that when compared to controls, individuals with schizophrenia who are treated with typical neuroleptics have larger basal ganglia, whereas those treated with atypical neuroleptics have decreased basal ganglia, caudate and lenticular nucleus (Corson, Nopoulos, Miller, Arndt, & Andreason, 1999). Structural evidence suggests that the basal ganglia may be damaged by the medication used to treat schizophrenia. Functional neuroimaging studies also reveal that the basal ganglia function abnormally in individuals with schizophrenia. SPECT and PET studies have suggested that in schizophrenia the basal ganglia have excessive amounts of dopamine because after administration of amphetamine, displacement of radioactive ligands binding to dopamine are released more than in controls (Laruelle et al., 1996). Thus, it appears that the basal ganglia are overactive in individuals with schizophrenia, most likely resulting from excess dopamine of antipsychotic medication used to treat schizophrenia.

Neurocognitive Deficits. Neurocognitive deficits are a direct expression of brain dysfunction and provided strong evidence for the presence of cerebral dysfunction long before current neuroimaging techniques were available. However, a challenge for neurocognitive research has been to identify differential deficits, (i.e., those deficits that are uniquely impaired) within the context of a more general and pervasive pattern of diminished cognitive abilities often observed in schizophrenia. These differential deficits

are of particular importance because they provide an indication of brain regions and neural circuits that are particularly susceptible in schizophrenia. Differential deficits consistently identified include memory, executive function, attention, planning and abstraction, which will be reviewed in the following sections.

Memory is viewed as one of the major cognitive deficits in individuals with schizophrenia and is often differentially impaired. Current prevailing theories of memory function have provided a variety of terms for various memory constructs. Some are relatively independent of each other, and others that substantially overlap. One of the oldest conceptualizations of memory is based on the duration of memory retention, and includes three primary memory stores, a sensory store, short-term store, and a long-term store. In the sensory store, information is accessible for milliseconds and is the first store in which information is registered. Relevant information from the sensory store is passed to the short-term memory store, which has a limited capacity (7 ± 2 pieces of information) and in which information is lost if not rehearsed after several seconds. Some information from the short-term store is passed to the long-term store, where it may remain indefinitely. In addition to these basic concepts, many other memory constructs have been identified, and some have been linked to specific brain regions. Figure 1 provides a schematic drawing of the different types of memory and the primary brain area associated with each type.

More recently, the concept of working memory has come to replace the construct of short-term memory. The working memory store is a short-term memory store in which information can be manipulated. Baddeley (1974) proposed three components in working memory, including the central executive, phonological loop and the visuospatial

sketchpad. As the name implies, the central executive is believed to control the phonological loop and the visuospatial sketchpad. The phonological loop codes acoustic information, while the visuospatial sketchpad codes visual information. Within long-term memory, there are two primary types: explicit (declarative) memory and implicit (non-declarative) memory. Explicit memory can be further subdivided into semantic and episodic memory (Tulving, 1989). Episodic memory refers to the autobiographical memories that a person has of what things or events have happened to them (Kolb & Whishaw, 2001).

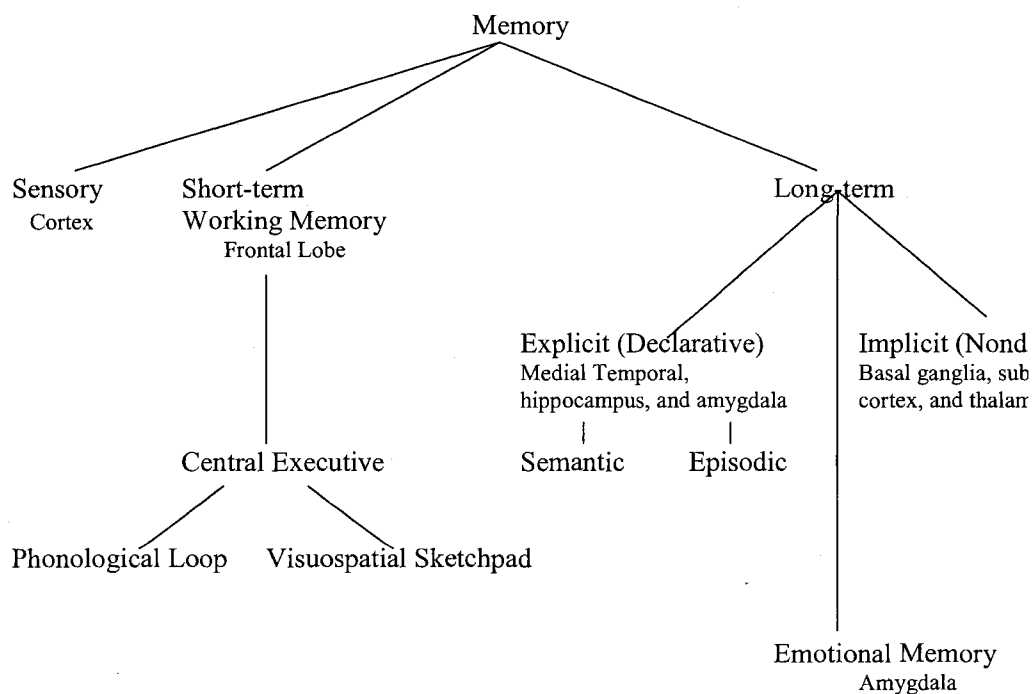
On the other hand, semantic memory is considered general knowledge or the ability to remember meanings and facts (Kolb & Whishaw, 2001). Implicit memory is learning without conscious knowledge. Implicit memory includes skills and habits, priming, classical conditioning and non-associative learning (reflexes). While emotional responses may fall under the heading of classical conditioning, many theorists have proposed that emotional memory may be another type of memory with components of explicit and implicit memory (Schachter, 1987). It may be assumed that some aspects of emotional memory rely on the implicit memory system (i.e., emotional “tagging” of life events) while others are consistent with explicit processing (i.e., remembering an emotional face).

These types of memory differ according to the type of thing to be remembered, and also in how and where they are processed in the brain. The entorhinal cortex, parahippocampal cortex, and the perirhinal cortex make up the medial temporal cortical regions (Kolb & Whishaw, 2001). This area, along with the hippocampus and the amygdala, is responsible for explicit memory. There is a reciprocal connection between

these areas and the neocortex. This builds and maintains a neural record. The amygdala seems to be the primary brain area responsible for emotional memory. The amygdala has very close connections to the medial temporal structures and the hypothalamus (Kolb & Whishaw). In implicit memory, the basal ganglia receive input from the entire cortex and the substantia nigra, which is rich in dopamine, and then sends projection to the ventral thalamus and then to the premotor cortex. While, the frontal lobe has connections to the medial temporal regions, it does not play a large role in explicit or implicit memory.

Figure 1

Graphic description of the different types of memory and the underlying neurological structures (Adapted from Thompson, 2001).



The frontal lobe is the primary site for working memory. As such, working memory findings in regard to schizophrenia will be discussed in conjunction with findings regarding the neurocognitive function of the frontal lobes.

Aleman, Hijman de Haan, and Kahn (1999) conducted a meta-analysis of the memory deficits associated with schizophrenia and found that memory was significantly impaired. Long-term recall measures yielded a $d = 1.21$ effect size. Performance was improved in cue conditions, but still significantly different than controls. Nonverbal memory was also not as impaired as verbal memory, but both were still significantly worse in individuals with schizophrenia compared to controls. There were no differences in immediate versus delayed recall conditions. Sullivan et al., (1992) have suggested that the declarative memory deficits associated with schizophrenia may be related to poor organizational strategies. A recent meta-analysis of recognition memory suggests that recognition memory is significantly impaired in individuals with schizophrenia ($d = .76$) and that figural memory is more impaired than verbal memory (Pelletier, Achim, Montoya, Lal & Lepage, 2005). Additionally, chronicity of the disease resulted in more memory impairment.

Individuals with schizophrenia also have deficits in attention as measured by such tasks as the CPT (Knight & Silverstein, 1998). The attention deficits seen in schizophrenia are so consistent that the CPT has also been proposed as a biochemical marker for schizophrenia. Longitudinal studies of individuals at risk for schizophrenia have found childhood deficits on CPT performance in those who later go on to develop schizophrenia (Cornblatt & Keilp, 1994; Nuechterlein, et al., 1992). Furthermore, the CPT can be used to differentiate individuals with psychosis or formal thought disorder

(Nelson, Sax & Strakowski, 1998). Poor performance on the CPT can be related to an impairment in contextual processing (Cohen & Servan-Schreiber, 1992), deficits in perceptual organization, or problems with working memory (Knight & Silverstein, 1998).

As expected, individuals with schizophrenia have difficulty on other measures of attention including the oddball task (Kogoj, Pirtosek, Tomori & Vodusek, 2005).

Individuals with schizophrenia also exhibit impairment on other neurocognitive tasks with an attentional component including digit span, spatial span, letter number sequencing, The Trail Making Test and the WCST (Heinrichs & Zakzanis, 1998).

During the oddball task, individuals with schizophrenia had difficulty-reorienting resources away from the primary task and were more susceptible to distraction than controls (Laurens, Kiehl, Ngan, & Liddle, 2005). Individuals with schizophrenia are consistently found to exhibit impairment on attentional measures.

The structural and functional deficits in the prefrontal cortex can cause impairment of executive function and working memory abilities (Baare et al., 1999). Executive function includes planning, abstraction, working memory, and decision-making. On the Wisconsin Card Sort Test, a measure of executive function, individuals with schizophrenia make more perseverative errors and achieve fewer categories correct (Goldberg, Torrey, Gold et al., 1995). Individuals with schizophrenia are also impaired on many other measures of executive function including The Trail Making Test B and the Stroop (Liddle and Morris, 1991). Individuals with schizophrenia have shown impairment on some of the most sensitive measures of abstraction and problem-solving including the Halstead Category Test, Part B of the Trail Making Test and the Halstead Tactual Performance Test (Goldstein, 1990). Verbal fluency is another measure of

executive function that is impaired in individuals with schizophrenia (Allen, Frith, & Liddle, 1993). Allen, Frith, and Liddle (1993) further suggest that the verbal fluency deficits associated with schizophrenia do not reflect the number of words stored, but the ability to access stored words. Working memory is the last category of cognitive tests representative of frontal lobe function. Working memory deficits have also been noted in individuals with schizophrenia (Fleming, Goldberg, Gold and Weinberger, 1995; Spindler, Sullivan, Menon, Lim, and Pfefferbaum, 1997; Sullivan, Shear, Zipursky, Sagar and Pfefferbaum, 1997), although it has been less clear which component of working memory was impaired. Spindler et al. determined that the working memory deficits seen in schizophrenia were the result of failure in multiple independent systems, rather than a problem with the central executive. Fleming and colleagues determined that working memory deficits are associated with limited processing resources. Contrary, to Spindler et al., Fleming et al. believed that the deficit in working memory was accounted for by a central executive because even during distractor tasks that could be considered semiautomatic, like counting, individuals with schizophrenia were more impaired than controls. Also of note, Fleming et al. found that individuals with schizophrenia made significantly more intrusion errors than controls. For working memory tests, as task difficulty increases, patients with schizophrenia attempt to compensate for neurological deficiencies by utilizing additional brain areas (Callicott, Bertolino, Mattay et al., 2000). It has also been suggested that the deficits in the prefrontal cortex of individuals with schizophrenia may contribute to explicit memory impairment (Goldman-Rakic, 1991). Overall, individuals with schizophrenia have impairment in a wide range of executive functions.

Basal ganglia impairment would be presumed to contribute predominantly to impairment in motor tasks. It could, however, be hypothesized that basal ganglia impairment may contribute to poor performance on measures of frontal lobe activity. The literature does show that individuals with schizophrenia do poorly on tests of motor function including finger tapping and The Trail Making Test A (Yang et al., 2004; Muller et al., 2002).

In conclusion, individuals with schizophrenia exhibit a wide range of neuropathological and neurocognitive deficits. There is a reduction in the whole brain volume and grey matter volume in individuals with schizophrenia. Individuals with schizophrenia also lack normal brain asymmetry. Structural imaging studies have found that the hippocampus, anterior cingulate, amygdala, and frontal lobes are smaller in individuals with schizophrenia than in those without schizophrenia. There is also evidence to suggest that the neuronal formations are different in individuals with schizophrenia, particularly in the hippocampus. Functional imaging studies indicate decreased function in the hippocampus, amygdala and frontal lobes, while the anterior cingulate appears to have increased activation in individuals with schizophrenia. Neurocognitive tests reveal impairment across memory function, executive function, attention, emotional processing, and motor function in those with schizophrenia.

Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is the most common diagnosis given to individuals who have been exposed to a traumatic event. Individuals with PTSD often alternate between feeling numb and detached from others to being flooded with emotion.

To qualify for a diagnosis of PTSD people exposed to a traumatic event must also experience some symptoms of hyperarousal, avoidance, and memory intrusions.

Sixty percent of Americans will be exposed to a traumatic event in their lifetime with many of those experiencing more than one traumatic event (Kessler et al., 1995). Identification and treatment of people who have experienced trauma and are having symptoms may help prevent the onset of PTSD. If untreated, 40% of people with PTSD symptoms in the wake of a traumatic event will go on to develop PTSD (Craine, Henson, Colliver & MacLean, 1988). Of those people with symptoms that received no treatment, remission time was increased from three to five years (Craine, Henson, Colliver & MacLean, 1988) and some may never recover (Friedman, 2001). Those individuals who continue to have symptoms may have more severe symptoms as time progresses and there is increased risk of developing secondary disorders (Nathan & Gorman, 2002). Current estimates of PTSD prevalence range from 5% to 14% in the United States (Breslau et al., 1998), with 8% generally agreed upon as the lifetime prevalence rate (Kessler et al., 1995).

A number of risk factors have been identified that predict who will or will not develop PTSD. Gender and type of trauma are usually considered the primary factors in determining who will develop PTSD after exposure to a traumatic event. In general, women are two times more likely than men to develop PTSD. Gender also influences the kind of traumatic event that one may experience. For example, men are most likely to experience trauma by witnessing a crime, being involved in an accident, or being threatened with a weapon. On the other hand, women are most likely to have been a witness to a crime, to be involved in an accident or to be molested.

The type of trauma experienced is also associated with different rates of PTSD. For example, witnessing a traumatic event and surviving a natural disaster have lower rates of PTSD than trauma involving personal attacks. One potential explanation for higher rates of PTSD associated with personal attacks is that they are directed at the individual. Also when a natural disaster occurs there are usually groups of people who were all exposed to the traumatic event at the same time allowing for more social support and communication, which can aid in healing. Within the types of trauma that involve personal attacks, torture survivors (Nathan & Gorman, 2002) and rape survivors have the highest rates of PTSD (Kessler et al., 2000). Broken down according to gender, rape is identified as the most traumatic event for both men and women (Kessler et al., 1995). There is also evidence to suggest that those individuals exposed to chronic trauma or that have been traumatized on more than one occasion are more likely to exhibit PTSD symptoms (Allen, 1995).

Other well-cited factors influencing the development of PTSD are the severity of the abuse, history of abuse, lower intelligence, earlier age at time of trauma, lack of social support, and genetic or personal history of psychiatric disorder (Nathan and Gorman, 2002). The most predictive psychological factor leading to cognitive impairment is the victim reporting that she feared for her life during the traumatic event (Sheiman, 1999). Additionally, a close association with the perpetrator may also lead to more psychological impairment (Lawyer, Ruggiero, Resnick, Kilpatrick & Saunders, 2006).

In regards to determining who will develop PTSD, there are some researchers to suggest that individuals who develop PTSD may have had pre-existing neurophysiological deficits making them more susceptible to the development of PTSD.

For example, while many studies have found decreased hippocampal volume in adult survivors of trauma, it is unclear whether the decreased volume preceded the onset of the trauma or vice versa (Stein, Koverola, Hanna, et al., 1997; Villarreal, Hamilton, Petropoulos, et al., 2002). Two studies have provided some evidence suggesting that hippocampal shrinkage may be a direct long-term effect of stress. The first study did not find loss of hippocampal volume in children with PTSD (DeBellis, Hall, Boring et al., 2001). The second study did not find any difference in hippocampal volume at 1 week or 6 months post-trauma suggesting that hippocampal reduction is not present prior to the onset of PTSD (Bonne et al., 2001). On the other hand, a study by Gilbertson et al., (2002) found decreased hippocampal volumes in noncombat twins of combat veterans with PTSD, suggesting that hippocampal volume may be a predisposition for development of PTSD. There is also research investigating whether differences in gamma amino butyric acid (GABA) may be present prior to the trauma and if they are predictive of who will develop PTSD. Vaiva et al., (2004) suggested that low levels of GABA may predict the onset of PTSD. Vaiva et al., measured plasma GABA levels immediately following traffic accidents and low GABA levels were correlated with higher Clinician Administered PTSD Scale (CAPS) scores. So, while there is still evidence to suggest that the physiological changes were present prior to the trauma and predictive of who will develop PTSD, the majority of the research suggests that physiological changes are a direct result of trauma.

As suggested in studies regarding chronic stress in animals, there are several changes that occur physiologically in response to stress that may be responsible for the associated cognitive deficits (Rasmusson and Charney, 1995). However, the

neuropathological and cognitive changes associated with stress have been more consistently identified in those with PTSD than in trauma survivors without a diagnosis of PTSD. The pathophysiological changes that occur after trauma may also be dependent on how severe or chronic the trauma, and the stage of development in the organism at the time when the trauma occurred. At this time, the underlying mechanisms contributing to the development of PTSD are unclear, as are how long after a trauma these changes persist. Fortunately, there is evidence to suggest that the physiological changes resulting from stress can be resolved with medication (Seedat, 2001).

In order to discuss the behavioral and cognitive changes resulting from a traumatic event, a discussion of the basic stress response will follow, with a discussion of the neurohormonal, neurotransmitter, and neurological changes associated with PTSD.

Stress Hormones, Neurotransmitters and PTSD

Cannon (1928) and Selye (1936) were the first to describe the impact of stress on an organism. They noted that the body would begin a series of reactions which may involve the cessation of current activity, most commonly termed the fight or flight response. Additional research has not only confirmed these effects, but has also included the sympathetic nervous system, hypothalamic-pituitary-adrenal axis (HPA), and endogenous opiates. Upon initiation of the fight-or-flight response the hypothalamus releases corticotropin releasing factor (CRF), which then activates the neurons in the locus coeruleus. CRF also mediates fear-related behavior and stimulates other neurochemical responses like the noradrenergic system (Bremner & Vermetten, 2001). The neurons of the locus coeruleus then activate the hypothalamus, amygdala, hippocampus and cerebral cortex. At the same time CRF released from the hypothalamus

will also stimulate the pituitary to release adrenocorticotrophic hormone (ACTH). ACTH then stimulates the adrenal gland to release cortisol, which will then have a negative effect on the axis at the pituitary and at the hypothalamus and hippocampus (Duman, 1995). This is the most discussed response to stress and is termed activation of the HPA axis. The HPA axis is then hyper-reactive, meaning that there are increased concentrations of CRF throughout the brain and spinal fluid (Arborelius, Owens, Plotsky & Nemeroff, 1999).

The aforementioned cascade of events has at least two important ramifications for PTSD. The first of which is that the stress response may somehow permanently alter the neurophysiology of the organism. If the adverse events are early, they can cause permanent damage to the HPA axis (Bremner & Vermetten, 2001). Long-term changes of the serotonergic system are associated with chronic stress, particularly in the hippocampus (Bremner & Vermetten, 2001). Even minor stressors have been documented to alter neuronal biology through activation of transcription factors (Daval, Nakajima, Gleiter, Post, & Marangos, 1989). As one might expect, cognitive and behavioral changes will accompany physiological changes associated with stress.

Individuals exposed to chronic stress or a more severe stressor (traumatic event) can experience cognitive, affective and behavioral changes that are attributed to the stress response (Arborelius, Owens, Plotsky & Nemeroff, 1999). Memory is the cognitive ability that is particularly susceptible to fluctuations in these neurochemicals. Peptides, like adrenocorticotrophic hormone (ACTH) and vasopressin, can strengthen memory, perhaps because of their role in long-term potentiation. Norepinephrine (NE) may strengthen or weaken the memory trace of the trauma and has direct input to the

amygdala. Administration of norepinephrine or epinephrine in animals increases recall of emotional material (Cahill & McGaugh, 1998). Adrenaline may strengthen memory traces at least temporarily (Elzinga & Bremner, 2002). On the other hand, cortisol may inhibit memory traces (Elzinga & Bremner, 2002). Overall, it has been shown that cortisol has a long-term effect of impairing memory (Kirschbaum et al., 1996). High levels of glucocorticoids can interfere with learning (Bremner & Vermetten, 2001). Memory and learning deficits may be mediated by other neurochemicals, including: brain-derived neurotrophic factor (BDNF), endorphins and oxytocin (van der Kolk, 1994). Neurohormonal changes then influence noradrenergic, serotonergic, gabaaminergic and dopaminergic neurotransmitters.

CRF interneurons are widely dispersed throughout the brain and are heavily concentrated in both the locus coeruleus and raphe nuclei, the origins for the noradrenergic and serotonergic pathways, both of which can be implicated in the behavioral and cognitive changes associated with PTSD (Arborelius, Owens, Plotsky & Nemeroff, 1999). Increased noradrenergic activity in the locus coeruleus increases over time resulting in behavioral sensitization. The overactive noradrenergic system resulting from stress is sensitive to even minor changes in the periphery of the body explaining the physical symptoms associated with anxiety in many individuals who have PTSD (Charney, Bremner, & Redmond, 2000). The noradrenergic response of the locus coeruleus can be associated with behavioral and cognitive changes after acute stress including: sleep problems, hypervigilance, irritability, anger and memory (Kimble & Kaufman, 2004).

The raphe nuclei are the location where the serotonergic system originates. There are efferents out to most of the brain, but serotonergic efferents are most heavily concentrated in the adrenergic and HPA system. The serotonergic system plays a significant role in learning and sensitization (Friedman, 2001). The serotonergic system is also implicated in depression, sleeping, eating and aggression. In PTSD, fear sensitization (Hensman et al., 1991) and depression (Davies et al., 1997) are the chief symptoms associated with the serotonergic system. While the serotonergic system has not received as much attention as the noradrenergic or gabaminergic system in PTSD, many of the available psychopharmacological treatments for PTSD will affect the serotonergic system.

The dopaminergic system has its origin in the substantia nigra and has efferents to the frontal cortex, substantia nigra, cerebellum, and temporal lobe. While the main function of the dopaminergic system is movement, dopamine is also the primary neurotransmitter in the brain's "reward center". The dopaminergic system in the medial prefrontal cortex also appears to be particularly sensitive to the effects of stress (Bremner and Vermetten, 2001) and should therefore exert the most influence on working memory and emotional responses. In PTSD, the behavioral symptoms of paranoia and hypervigilance may be mediated by the dopaminergic system.

Gamma-aminobutyric acid (GABA) has been widely discussed in conjunction with stress and PTSD. During acute stress, the number of GABA binding sites is reduced and benzodiazepine binding sites are increased (Horger & Roth, 1995; Bremner & Vermetten, 2001). When there is active physiological coping, GABA is enhanced, and emotional memory is impaired. When there is lack of coping (lack of physiological

response), GABA is reduced and emotional memory is especially vivid. This change in memory is because the GABA receptor has an anti-anxiety release receptor. Increases in GABA enhance release of the anti-anxiety compound. The GABA molecule has a binding site for sedative-hypnotics and benzodiazepines in addition to the GABA binding site. These two other binding sites on the GABA molecule may mediate some of the changes associated with stress. For example, it has been noted that taking a GABA-stimulating drug before the occurrence of a traumatic event can decrease the likelihood of developing PTSD (Maes et al., 2001). Studies have also shown that benzodiazepine binding may be able to cause a situational amnesia associated with stress. Results of animal studies indicate a decrease in benzodiazepine binding primarily in the frontal cortex and the hippocampus (Bremner and Vermetten, 2001). In humans, ligand neuroimaging, found a 41% decrease in benzodiazepine binding in individuals with PTSD (Bremner, Innis, Southwick et al., 2000). Decreases in benzodiazepine binding in the prefrontal cortex may be related to emotional processing, whereas decreases in benzodiazepine binding in the hippocampus could translate to memory difficulties. In conclusion, GABA appears to be a particularly important neurotransmitter for the cognitive and behavioral changes associated with stress.

Structural and Functional Brain Abnormalities in PTSD

The remainder of the PTSD section will go on to give a brief description of the primary tasks associated with the limbic system structures and the prefrontal cortex followed by a discussion of the relevant structural and functional changes associated with PTSD. The last section will be a discussion of the cognitive deficits associated with PTSD. The cognitive section will be broken down based on cognitive domains.

The Limbic System. The limbic system is responsible for our emotional responses, hormones, motivation, pain and pleasure sensation and memory. The limbic system is comprised of the hypothalamus, hippocampus, amygdala, cingulate gyrus, olfactory cortex, thalamus and fornix. It is believed that the noradrenergic response during the stressor influences the limbic system to be hypersensitive, thereby disrupting the normal activities of the limbic structures (Everly & Horton, 1998).

The hippocampus is an area of the brain that is involved in both memory and emotion. Since the hippocampus connects, organizes, and locates explicit memory, the stress caused by trauma may lead to a distortion or fragmentation of these memories (Bremner, 2002). The hippocampus is also responsible for dealing with the body's stress response, particularly in reducing cortisol levels (Bremner & Narayan, 1998). Both structural and functional abnormalities have been reported for the hippocampus in PTSD.

Magnetic resonance imaging studies (MRI) have revealed that survivors of rape suffering from PTSD have diminished right hippocampal volume (Stein, Koverola, Hanna, Torchia, & McClarty, 1997). Right hippocampal reductions were also found in recent trauma survivors with PTSD (Wignall et al., 2004). Left hippocampal reduction has been found in PTSD patients that were abused in childhood, while PTSD patients traumatized in adulthood had bilateral or right hippocampal atrophy (Seedat, 2002). Bremner, Randall, Vermetten et al., (1995) found an 8% reduction of hippocampal volume in veterans with PTSD. Subsequently, Bremner, Randall, Vermetten et al., (1997) found a 12% reduction of left hippocampal volume in people with PTSD due to childhood abuse as compared to people with a childhood abuse history without a diagnosis of PTSD. Gurvits et al., (1996) also found a reduction in hippocampal volume

for veterans with PTSD. There have been some studies that have not found a difference in hippocampal volume in individuals with PTSD (Bonne, et al., 2001; Gilbertson et al., 2002; Neylan et al., 2004). Nutt and Malizia (2004) suggested that any null findings in regards to hippocampal volume and PTSD may be related to hemispheric differences. Nutt and Malizia hypothesized that patients with reductions in right hippocampal volume have more memory deficits whereas left sided deficits are associated with more dissociation. Overall, evidence suggests that hippocampal volume is reduced in individuals with PTSD.

Functional brain imaging studies of the hippocampus and associated areas in individuals with PTSD have also yielded some interesting results. Bremner et al., (1999) found decreased cerebral blood flow in the right hippocampus and supramarginal gyrus of individuals with PTSD. The PET scans utilized a neutral script and a personalized account of the individual's childhood abuse. Conversely, Shin et al., (1999) found increased cerebral blood flow in the anterior temporal poles in individuals with a trauma history using similar stimuli. The PTSD group experienced the greatest increases in the anterior temporal pole (Shin et al., 1999). Overall, the functional differences in the medial temporal lobe of individuals with PTSD are not as strong as the structural findings.

The amygdala is the primary structure in emotional memory. The amygdala assigns feelings of significance to sensory input and then the neocortex elaborates and assigns personal meaning (van der Kolk, 1994). Studying the amygdala is difficult because while the amygdala may be responsible for encoding the specific

autobiographical trauma material it may not be responsive to general trauma material or during retrieval of trauma material (Hull, 2002).

The structural findings regarding the amygdala in PTSD are inconclusive. Bremner et al., (1997) found that survivors of childhood sexual abuse with PTSD had a trend towards larger amygdala. Wignall et al., (2004) performed a structural analysis of people recently exposed to a traumatic event with PTSD and did not find any differences in the size of the amygdala. Bremner et al., (1997) did not find any structural differences in the size of the amygdala in adult survivors of childhood abuse with PTSD. Teicher et al., (2002) found reductions in the size of the amygdala. Matsuoka, Yamawaki, Inagaki, Akechi, and Uchitomi (2003) found smaller amygdala in cancer survivors with intrusive thoughts. The majority of structural findings have found no difference in the size of the amygdala in individuals exposed to a traumatic event.

Functional findings regarding the amygdala show that the amygdala is hyper-responsive to fearful stimuli in PTSD. Positron emission tomography (PET) scans have revealed that the amygdala is exceptionally active while the survivor is reliving the traumatic memory (Emilien, Penasse, Charles, Martin, Lasseaux & Waltregny, 2000). Using a masked face paradigm and fMRI, Rauch et al., (2000) could distinguish those people with and without PTSD based on the magnitude of the amygdala response with 75% sensitivity and 100% specificity. Several studies have noted right-sided activation of the amygdala in individuals with PTSD during recall of traumatic material (Shin et al., 1997; Rauch 1996). Shin et al., (2004) found that female nurse veterans with PTSD did not have significant activation of the amygdala, but the male combat veterans did. Liberzon et al., (1999) found bilateral amygdala activation along with activation in the

other expected limbic areas utilizing auditory sound activation. The amygdala activation was specific to PTSD patients and did not occur in controls or in veterans without PTSD (Liberzon et al., 1999). Gilboa et al., (2004) utilizing a PET scan with rCBF analysis has shown that the intrusive re-experiencing in PTSD does not involve a failure of cingulate inhibition, but represents an overactive amygdala. Other studies have found no amygdala activation utilizing trauma probes (Bremner et al., 1999; Shin et al., 1999). These discrepancies may be due to the study design, type of trauma, or imaging techniques (Pissiota et al., 2002). Pissiota also suggests that the lateralization of fear activation in the amygdala may be related to perceptual (right) or cognitive representations (left). Overall, research suggests that the amygdala is overactive to traumatic stimuli in individuals with PTSD.

The cingulate gyrus is responsible for filtering memories and integrating sensory experience with cognitive experience. The anterior cingulate has been subdivided based on cytoarchitecture and connectivity into a dorsal, cognitive-motor division, a rostral, affective division, and a ventral, visceromotor division (Rauch et al., 2003). In PTSD, significant volumetric decreases have been found with MRI in the rostral and ventral parts of the anterior cingulate suggesting that although the amygdala is hyperresponsive to threat related stimuli, it is exacerbated by insufficient inhibition from the pregenual and subcallosal cortex (Rauch et al., 2003). Araki et al., (2005) also found decreases in the anatomical size of the anterior cingulate in individuals with PTSD from a Tokyo subway attack. The decreased anterior cingulate volume was correlated with lower P300 amplitudes in an oddball task (Araki et al., 2005). Neuronal loss in the anterior cingulate was also found in a study of children with PTSD (DeBellis, Keshaven, Spencer, Hall,

2000). Although there are only a limited number of studies, they all suggest a decrease in the volume of the anterior cingulate.

Functional imaging studies reveal hypoactivation in the anterior cingulate. Hull (2002) found decreased activation in the anterior cingulate, potentially explaining the reason why people with PTSD are unable to extinguish fear. Yang, Wu, Hsu, and Ker (2004) did not find activation of the anterior cingulate in earthquake survivors with PTSD, while those earthquake survivors without PTSD had activation of the anterior cingulate. Bremner et al. (2004) found that women with abuse related PTSD had a decrease in anterior cingulate blood flow on PET scan during the Emotional Stroop task. Shin et al., (2001) found that the PTSD group had a diminished response of the rostral anterior cingulate in response to traumatic stimuli. While the anterior cingulate is not especially active in patients with PTSD the posterior cingulate is (Hull, 2002). The activation of the posterior cingulate may be related to processing emotional information. Accordingly, Lanius et al., (2004) found that the patients with PTSD had greater activation in the posterior cingulate gyrus, while those people without PTSD had greater activation in the anterior cingulate gyrus. PET studies have also revealed increased activation of the posterior cingulate and motor cortex without activation of the medial prefrontal cortex and anterior cingulate in women that had histories of child abuse when read a script of the abuse (Shin, McNally, Kosslyn et al., 1999). While most studies suggest that the anterior cingulate contributes to PTSD by it's inability to regulate the amygdala, Gilboa et al., (2004) using a functional path analysis determined that the anterior cingulate in PTSD is related to the "modulation of the structures involved in

autonomic control rather than the amygdala itself". Results of physiological studies indicate that the anterior cingulate is a core component in PTSD.

Medial Prefrontal Cortex. The other brain area implicated in many of the symptoms experienced by trauma survivors is the medial prefrontal cortex. The medial prefrontal cortex is attributed with regulating emotional responses, inhibiting competing memories, planning, organization, filtering and inhibition. Collectively many of the tasks performed by the medial prefrontal cortex are termed executive function.

There is no research to suggest that there are structural alterations in the prefrontal cortex in individuals with PTSD. The functional findings regarding the prefrontal cortex are, however, the most replicated physiological finding in PTSD (Bremner, 2002). Gilboa et al., (2004) have determined that in individuals with PTSD the amygdala exerts greater influence over the medial prefrontal cortex than in those without PTSD. "Women with abuse related PTSD had a decrease in medial prefrontal blood flow during recall of stressful word pairs" (Bremner et al., 3/1/01 as cited in Bremner and Vermetten, 2001). SPECT studies have shown an increased regional cerebral blood flow (rCBF) in the medial prefrontal cortex during traumatic provocation in patients with PTSD (Hull, 2002). Shin et al., (2004) directly tested the relationship between the amygdala and medial prefrontal regions during provocation and found that amygdala activation and medial frontal gyrus activation were negatively correlated in nurses and combat veterans (Shin et al., 2004). CAPS scores could significantly predict these patterns of activation even after controlling for depression. Studies have found abnormal frontal slow-wave activity using ERP during assimilation of new information in working memory in patients with PTSD (Galletly et al., 2001). PET studies (Clark et al., 2003) show that unlike

controls, PTSD patients do not have left activation of the inferior parietal lobe and the dorsolateral prefrontal cortex during working memory updating, suggesting that PTSD patients do not use symbolic representation. There was however, increased activation of the posterolateral aspect of the superior parietal lobe indicating more reliance on visuospatial coding (Clark et al., 2003). An interesting replicated finding of note, is the deactivation of Broca's area (Rauch et al., 1996; Shin et al., 1997). The deactivation of Broca's area may contribute to the difficulty people with a history of trauma have in restructuring their experience (Hull, 2002). Overall, the most robust physiological finding associated with PTSD is hypoactivity in the pre-frontal cortex.

Neurocognitive Function. Over 50% of sexually abused patients experience memory intrusions and memory impairment (Craine, Henson, Colliver, & MacLean, 1988). Typical complaints from trauma survivors are problems with memory, learning, attention, and concentration (Palmer et al., 1999). Clinicians have noted deficits in planning, organization, and judgment (Palmer, Frantz, and Armsworth, 1999). Severity of PTSD has been correlated with overall inconsistency of memory (Zoellner, Sacks, & Foa, 2001). This is typically characterized by an inability to remember parts of the trauma (autobiographical). For example, sixty-four percent of raped females have had some amnesia (Herman & Schatzow, 1987). Archibald and Tuddenham (1965) documented memory loss regarding combat in WWII veterans.

Studies have found working memory, explicit general memory, and to a smaller extent implicit memory deficits in survivors of trauma (Jenkins, Langlais, Delis, & Cohen, 1998; McNally et al., 1998; Williams, Bremner et al., 1995). Severe autobiographical memory deficits (amnesia) in rape survivors have been demonstrated by

Williams (1995) who contacted women that had been in the hospital 17 years prior to questioning for sexual abuse. Of these 129 women 38% did not recall the incident. Other studies regarding general explicit memory have found greater disturbance in those people with PTSD than those participants without PTSD (Jenkins, Langlais, Delis & Cohen, 1998). Utilizing the California Verbal Learning Test, PTSD patients had significant impairment in long-delay recall and short- delay recall compared to those trauma survivors without PTSD or controls. The deficits found in explicit memory were not due to differences in learning strategy as measured by the semantic and serial clustering indices. Since the performance differences could not be accounted for by learning strategies, IQ differences, or presence of substance abuse, Jenkins, Langlais, Delis & Cohen suggested that the differences in explicit memory were due to the presence of PTSD. Vasterling, Brailey, and Sutker (2000) found that veterans with PTSD were impaired on measures of verbal learning, but not other measures of dorsolateral prefrontal and medial temporal functioning as compared to veterans without PTSD (Vasterling, Brailey & Sutker, 2000).

Using the Wechsler Memory Scale (Russel, 1978) and the verbal Selective Reminding Test (vSRT; Hannay & Levin, 1985) Bremner et al., (1993, 1995) found deficits in verbal declarative memory in combat veterans with PTSD and in PTSD patients with childhood abuse. The amount of impairment was associated with the severity of abuse. Yehuda, Golier, Halligan and Harvey (2004) have shown that Holocaust survivors with PTSD exhibited verbal learning deficits after controlling for IQ on the CVLT. The memory differences are due to total learning and may reflect a limit in memory capacity. Other studies like the one by Neylan et al., (2004) found no relation

between hippocampal n-acetylaspartate (NAA) levels and memory using the CVLT and portions of the WMS-III. They also found no difference in cognitive function between the veterans with PTSD and those without. The treatment criteria in this study were very stringent and ruled out any patient that had another comorbid disorder in the past three months, substance abuse in the past five years, any patients with head trauma or those that had taken benzodiazepines or antipsychotic medication in the last 6 weeks (Neylan et al., 2004). In conclusion, it appears that individuals with PTSD experience deficits in verbal explicit memory.

Being that the physiological findings regarding the prefrontal cortex in PTSD are the most robust, we would expect to see consistent results in regards to the cognitive tests for this area. Tests for the prefrontal cortex include measures of attention, planning, set shifting, and working memory. Victims of intimate partner violence, regardless of PTSD status, performed poorly on tasks of sustained attention, working memory, and response inhibition (Stein, Kennedy, Twamley, 2002). Felmingham, Bryant and Kendall (2002) and Akari et al., (2005) have found reduced latencies in search time during the oddball task in individuals with PTSD, suggesting that individuals with PTSD may have increased difficulty in discriminating and attending to particular stimuli. Similarly, Semple et al., (1996) noted that combat veterans had more false alarms on the auditory continuous performance task. Golier et al., (1997) did not find any difference in performance on the CPT in individuals with PTSD. It is unclear whether individuals with PTSD experience more difficulties with attention than individuals not exposed to trauma. These studies suggest that a trauma history is associated with poorer performance on attention measures.

Gilbertson, Gurvits, Lasko, Orr and Pitman (2001) have noted impairments in executive function in combat veterans with PTSD. Specifically, the PTSD group had significant impairments on the digit span of the WAIS-R, Trail Making Test B, and WCST categories, perseverative responses and nonperseverative errors. Sutker et al., (1991) also identified deficits in executive function on the Categories Test and the WCST. On the other hand, Vasterling et al., (1998) did not find any differences in the WCST, digit span of the WAIS-R or on the Stroop in a sample of veterans. Therefore, results of cognitive testing for prefrontal functioning are not as convincing as the functional imaging data, particularly in the executive function domain.

In addition to the subjective emotional reports and physiological arousal identified in individuals with PTSD, there have recently been some empirical studies on emotional processes. There have been deficits associated with the congruence of facial expression and self-report of emotion in women who had PTSD after being sexually assaulted (Wagner, Roemer, Orsillo, Litz, 2003). Bremner et al., (2003) performed PET while asking patients to remember neutral or traumatic word pairs. Deeply encoded neutral words were recalled better than deeply encoded negative words, which were both better than shallowly encoded words. This was the same pattern for people with PTSD and controls. The pattern of activation only differed between the two groups when retrieving emotionally valenced words. Michael, Ehlers and Halligan (2005) found that assault survivors with PTSD had increased priming for trauma-related words compared to assault survivors without PTSD. There is increasing evidence to suggest that trauma survivors experience cognitive deficits in emotional processing.

Exposure to a traumatic event may cause enough stress to an individual to precipitate behavioral and affective changes. The neurochemical changes can result in changes to the brain structures and function. While not consistently found, evidence suggests that individuals with PTSD exhibit decreases in hippocampal volume. There is also neuronal loss in the anterior cingulate resulting in decreased volume. Functionally, the amygdala is hyperresponsive, while the medial prefrontal cortex is hypoactive. The neurocognitive deficits most commonly found in PTSD are problems with explicit memory. These findings provide support for the proposition that stress and trauma cause alterations to brain structure and function.

Comorbid Schizophrenia and PTSD

The following section will be a discussion of comorbid schizophrenia and PTSD. It will include information regarding prevalence and diagnosis, followed by a discussion of the impact that trauma may have on those with mental illness and a review of two models proposed to explain the high rates of comorbidity and the increase of psychiatric symptoms between the two disorders. There have not been any studies to examine the structural, functional or neurocognitive findings associated with PTSD in individuals with schizophrenia, so there will be a discussion of three potential models to address the pattern of neurocognitive deficits associated with comorbid schizophrenia and PTSD.

Prevalence

Rates of trauma. Studies suggest that the rate of traumatic events in individuals with severe mental illnesses is higher than in the general population. For example, 43% to 81% of individuals with severe mental illness have been exposed to either physical or sexual interpersonal violence (Hutchings & Dutton, 1993; Jacobsen, 1989; Lipschitz et

al., 1996). Another large multi-site study (n=782) of victimization in those with severe mental illness found 87% of the sample had been victimized in some way (Goodman et al., 2001). Women were much more likely to have been sexually assaulted, while men were more likely to have experienced physical assault (Goodman et al., 2001).

Childhood abuse has been reported in 34% to 53% of individuals with severe mental illness (Craine, Henson, Colliver & MacLean, 1988; Greenfield et al., 1994; Mueser et al., 1998; Ross et al., 1994). As documented in these studies, the rates of traumatic events in individuals with schizophrenia are higher than in the general population.

Recent victimization is also more prevalent in people with severe mental illness than in the general population. Seventy-nine percent of individuals with severe mental illness have been victimized within the last year (Cascardi, Mueser, DeGirolomo, & Murrin, 1996) and 33% of mentally ill homeless women had been sexually or physically assaulted within the last 30 days (Goodman, Dutton, & Harris, 1997). As noted above, those individuals who are homeless and have a severe mental illness have even higher rates of interpersonal violence than non-homeless individuals with severe mental illness. Goodman et al. (1995) and Davies-Netzley et al. (1996) found that between 77% and 97% of homeless individuals with severe mental illness experienced interpersonal violence. Another subset of individuals that may be particularly susceptible to traumatic events is those individuals with schizophrenia who also abuse substances (Gearon, Kaltman, Brown & Bellack, 2003).

Many individuals with severe mental illness will also be exposed to multiple traumas (Mueser, Goodman, & Trumbetta, 1998). Goodman et al. (2001) reported that revictimization rates were particularly high with 67% of the sample reporting abuse in

childhood and adulthood. These revictimization statistics may be accounted for by the fact that there is an increased rate of multiple traumatization in the general population when individuals were abused as children or with people who have been sexually assaulted (Classen, Palesh, Aggaral, 2005; Vrana & Lauterbach, 1994). Briere et al. (1997) replicated the relationship between childhood sexual abuse and adult victimization in a sample of psychiatric inpatients with severe mental illness. They did not find the same relationship in these patients when the childhood abuse was physical abuse rather than sexual abuse. In a sample of substance abusing women with schizophrenia the average number of traumatic events reported was eight (Gearon, Kaltman, Brown & Bellack, 2003). As might be expected, revictimization is associated with greater PTSD symptom severity (Follette et al., 1996).

As with non-mentally ill patients, different types of trauma are associated with different rates of PTSD. A regression analysis of female psychiatric inpatients with severe mental illness indicated that both child and adult assaults were associated with psychiatric difficulties, with childhood sexual abuse was the most powerful predictor of psychiatric difficulties even after controlling for demographic variables (Briere et al., 1997). Gearon et al., (2003) found that sexual abuse was the type of trauma associated with the highest levels of PTSD symptoms. Similarly, in a study by Mueser et al., (1998) childhood sexual assault was the strongest predictor of PTSD for both men and women, but women who were physically attacked and witnessed a killing or severe injury in childhood were also prone to develop PTSD. In adulthood, women who were sexually assaulted or witnessed a killing or serious injury were prone to PTSD, while there was no specific trauma type for men that was most likely to cause PTSD (Mueser et al., 1998).

In conclusion, the number of traumas experienced and being sexually abused as a child are significant predictors of PTSD and are also predictive of adult victimization in individuals with severe mental illness (Mueser et al., 1998).

Rates of PTSD. As might be expected, the prevalence rates for diagnosis of PTSD are also much higher in individuals with severe mental illness. Six studies assessing PTSD in individuals with severe mental illness found 29% to 43% of their sample qualified for diagnosis of PTSD, which is in sharp contrast to a rate 8% as observed in the general population (Mueser, Salyers, Rosenberg, Ford, Fox, & Carty, 2001). Another study documented a diagnosis of PTSD in 66% of their sample of individuals with severe mental illness (Craine, Henson, Colliver and MacLean, 1988). None of these participants had received treatment related to their trauma symptoms. Mueser et al. (1998) found 43% of the individuals with schizophrenia in their sample qualified for diagnosis of PTSD and had similarly not received treatment for trauma symptoms.

Individuals with schizophrenia who also have another comorbid disorder, such as substance abuse, may be particularly susceptible to developing PTSD after experiencing trauma. In particular, in individuals with comorbid substance abuse and schizophrenia, Gearon et al. (2003) found that 46% of their sample of women with comorbid substance abuse and schizophrenia had PTSD. Once again, 46% is much higher than the rate of PTSD in the general population (8%) or the rate of PTSD in individuals with schizophrenia (around 30%) or the rate of PTSD in substance abusing women (30%).

Despite the high prevalence of trauma and subsequent PTSD in those with severe mental illness, PTSD is still widely under-diagnosed in this population (Craine, Henson, Colliver, & MacLean, 1988). In a review of six studies assessing rates of PTSD in

individuals with severe mental illness, only 5% of those patients that qualified for a diagnosis of PTSD actually had a diagnosis of PTSD in their chart (Mueser et al., 2001). One study found that of those individuals with schizophrenia that had been traumatized 38% had not discussed it with a counselor, 36% had never told a friend or family member and 28% had told no one other than the interviewer (Resnick, Bond & Mueser, 2003). Two other studies described above documented rates of untreated PTSD in 66% and 43% of their samples (Mueser et al., 1998; Craine, Henson, Colliver, & Maclean). Thus, identifying those patients with a history of prior trauma is crucial in identifying those at risk for re-traumatization, as well as, identifying those at risk for developing PTSD.

Impact of Trauma on Schizophrenia Outcomes. Research has clearly demonstrated the negative impact of trauma on mental illness. The presence of trauma in individuals with schizophrenia is correlated with increased psychiatric disturbance and poorer functional and treatment outcomes. Craine, Henson, Colliver and MacLean (1988) found that individuals with severe mental illness who had been sexually abused exhibited significantly more symptoms commonly linked to sexual abuse (e.g. compulsive sex behavior, crying, low energy) than in those without a history of abuse suggesting that trauma causes additional symptoms that are distinct from the symptoms associated with chronic illness alone and are more reflective of PTSD symptoms. Read and Ross (2002) also noted that individuals with severe mental illness and a history of childhood abuse had more general psychiatric symptoms. In individuals who have schizophrenia and comorbid substance abuse, revictimization was associated with greater PTSD symptom severity as measured by the Clinician Administered PTSD Scale (CAPS) (Resnick, Bond & Mueser, 2003). Resnick, Bond and Mueser (2003) found that in

individuals with schizophrenia, hyperarousal, emotional discomfort and avoidance as measured by the CAPS were highly correlated with the presence of a traumatic event. There was a consistent relationship between the severity of trauma and severity of PTSD symptoms among women. The avoidance subscale, in particular, was significantly correlated with the positive symptoms on the Positive and Negative Syndrome Scale (PANSS) suggesting that the avoidance of trauma-related stimuli may exacerbate positive symptoms of schizophrenia.

History of childhood abuse also appears to increase positive symptoms typically associated with schizophrenia in those who are not diagnosed with the disorder. In accordance, Ross, Anderson and Clark (1994) found more positive symptoms of schizophrenia in those with a history of childhood abuse. In a college sample without schizophrenia, Ross and Joshi (1992) found that the number of Schneiderian symptoms endorsed was significantly correlated with a history of abuse, the number of perpetrators and the number or types of sexual abuse experienced. Mullen et al., (1993) found that women who had experienced any type of sexual abuse were 5.4 times more likely to have been a psychiatric inpatient. These numbers increased to 16.8 when penetration occurred. Childhood sexual abuse survivors also had significantly higher scores on the neuroticism scale on the NEO Five Factor Inventory (Costa & McCrae, 1989). These findings suggest that childhood trauma can predict an increase in schizophrenia-like psychiatric symptoms regardless of prior psychiatric history.

A trauma history also suggests poorer functional and treatment outcomes in individuals with schizophrenia. Lysaker, Meyer, Evans, Clements, and Marks (2001) found that individuals with schizophrenia who were also survivors of childhood abuse

had significantly poorer scores on instrumental role and intrapsychic foundations subscales of the Quality of Life Scale (Heinrichs, Hanlon, & Carpenter, 1984) reflecting impairments in the quality of their relationships. Individuals with schizophrenia and a trauma history are more likely to have comorbid substance abuse and to be homeless (Goodman, Rosenberg, Mueser & Drake, 1997; Mueser, Goodman, Trumbetta, Rosenberg, Osher, Vidaver, Auciello, & Foy, 1998). Individuals who have experienced childhood abuse and also have schizophrenia are more likely to attempt suicide, receive more medication, have longer hospitalizations, and have an earlier first admission for psychiatric treatment (Read & Ross, 2003). Recent assault also contributes to recent homelessness, alcohol and drug use, more hospitalizations in the last year, and an earlier first age of psychiatric hospitalization (Goodman et al., 2001). Rates of PTSD were dramatically higher in forensic patients with paranoid schizophrenia (52%) versus 29% in a non-offender population of patients with paranoid schizophrenia (Sarkar, Mezey, Cohen, Singh, & Olumot, (2005). Despite the implications of trauma for those individuals with schizophrenia, research regarding traumatic events in the lives of those with schizophrenia has been sparse and PTSD remains under-diagnosed in schizophrenia (Sanislow & Carson, 2001).

Diagnosing PTSD in Schizophrenia. One factor that contributes to the under-diagnosis of PTSD and schizophrenia, possibly limiting research attempts thus far, is the practical question of accurately assessing PTSD symptoms in individuals with severe mental illnesses. Some have suggested that because the nature of schizophrenia involves distortions of reality, it is unclear whether the memory of a traumatic event is as reliable as an individual without schizophrenia. A study examining the reliability of child abuse

reports by Fergusson, Horwood and Woodward (2000) using a large (N=1265) birth cohort found that reports of abuse in controls was relatively unstable with a test-retest kappa value of .45. The instability of reporting reflected an underreporting of traumatic events. Fergusson, Horwood, and Woodward (2000) also found that inconsistencies in reporting were not related to psychiatric state, suggesting that the severely mentally ill can be reliably evaluated. Other studies have found fair to moderate test-retest reliability in patients with and without severe mental illness (Goodman, Cocoran, Turner, Yuan, & Green, 1998, Goodman, et al., 1999). Goodman et al. (1999) demonstrated that individuals with severe mental illness had similar percentages for the consistency of self-reported trauma (86% in individuals with severe mental illness versus 85% in the student sample for adult physical abuse and 97% versus 80% for childhood abuse) over a two week period as a student sample. The self-report of PTSD symptoms in patients with severe mental illness also had a good reliability with a test-retest correlation of .81 at two weeks (Goodman, 1999). Convergent validity of PTSD diagnosis by interview and self-report measures using strict PTSD criteria was $k = .90$ (Mueser et al., in press). Test retest of the CAPS and PTSD checklist (PCL; a measure of PTSD symptoms) were also significant at .77 and .66 indicating high reliability for both self-report and interview assessment of PTSD symptoms. Mueser et al. (2001) found a mean inter-rater reliability of .96 between the CAPS and the Trauma History Questionnaire (a self-report questionnaire asking the individual to state if they had experienced each type of trauma and when the trauma occurred) in individuals with severe mental illness suggesting that measurements used in other samples could reliably be used with individuals who have severe mental illnesses. Internal consistency was also high at .94 (baseline) and .95

(follow-up). Kappa values were at approximately .60 for the most prevalent types of trauma indicating moderate to high test-retest reliability of trauma reports and PTSD diagnosis. The kappa values were lower at .36 and .43 for life-threatening illness and the death of a friend or relative.

Models Proposed to Explain Comorbidity Between Schizophrenia and PTSD.

There are two theories proposed to account for the high comorbidity between schizophrenia and PTSD. The first of these is the traumagenic neurodevelopmental model (Read, Perry, Moskowitz and Connolly, 2001). The traumagenic neurodevelopmental model suggests that some individuals with schizophrenia may have had an early traumatic event that could trigger the onset of schizophrenia symptoms and may cause or contribute to the neurodevelopmental abnormalities seen in schizophrenia. Or, put another way, they would posit that schizophrenia is a trauma based disorder. As support for their model Read, Perry, Moskowitz and Connolly (2001) have cited the similarities between the effects of traumatic events on the brain and the biological abnormalities associated with schizophrenia. In particular, these biological abnormalities include over-reactivity of the hypothalamic-pituitary-adrenal (HPA) axis, neurotransmitter abnormalities, and structural changes to the brain.

The second major area of support delineated by the authors for the traumagenic neurodevelopmental model comes from studies of the environmental influence in schizophrenia. For example, environmental influences like family hostility (Tarrier & Turpin, 1992), adoptive studies (Tienari, 1991) and other environmental stressors in utero. Read et al. (2001) reported that adoptive families had 7 times more explanatory power than genetics in predicting who would develop schizophrenia. Furthermore

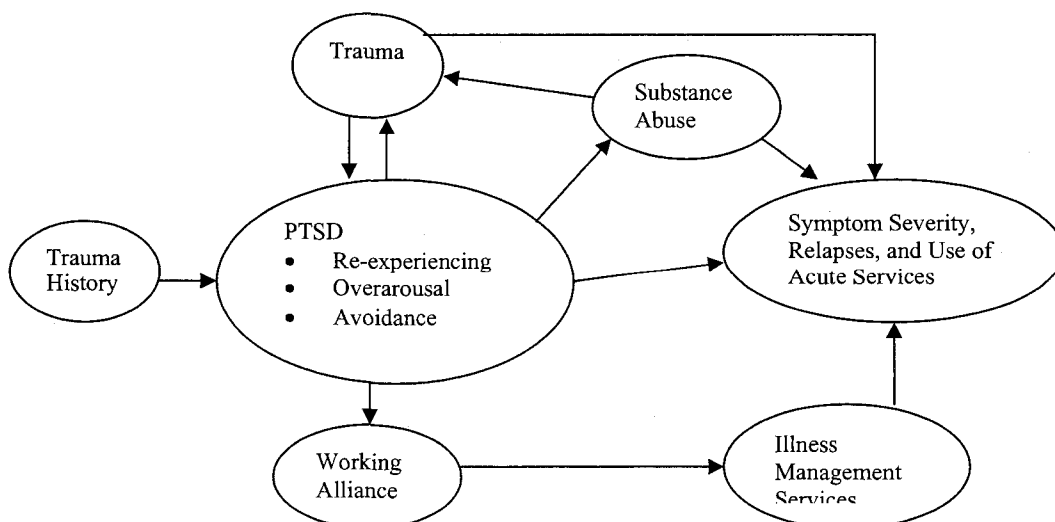
children living in an institution are 2.7 times more likely to be diagnosed with schizophrenia as adults than children living at home (Canon et al., 2001). Other environmental stressors like traumatic brain injury have also been linked with schizophrenia (Malaspina et al., 2001). Malaspina documented that 17% of adults diagnosed with schizophrenia have had a traumatic brain injury. There is some evidence that would be contrary to the traumagenic model posited by Read, Perry, Moskowitz, and Connolly (2001). For example, Rosenberg et al. (2001) suggested that individuals with severe mental illness report higher rates of trauma in adulthood rather than in childhood. This would remove the possibility of schizophrenia being caused by a traumatic event in the individuals traumatized in adulthood after the emergence of schizophrenia.

The other model suggests that there is an interaction between PTSD and schizophrenia such that individuals with schizophrenia may be more susceptible to traumatic events or to the psychological effects of trauma because of the deficits associated with schizophrenia (Mueser, Rosenber, Goodman & Trumbetta, 2002). For example, people with schizophrenia are more likely to be homeless or to use substances than the general population and both of these variables are associated with increased rates of traumatic exposure (Goodman, Rosenberg, Mueser & Drake, 1997; Mueser, Goodman, Trumbetta, Rosenberg, Osher, Vidaver, Auciello, & Foy, 1998). Research has also documented that individuals with a history of childhood sexual trauma have poorer vocational performance (Lysaker, Nees, Lancaster, & Davis, 2004). On the other hand, mental illness may also be a predictor of who will develop PTSD, such that an individual may be more likely to develop PTSD after a traumatic event if they are exposed to a traumatic event. Research citing increased rates of developing PTSD in people with a

history of psychiatric history would support this assertion (Breslau et al., 1995). The interactive model also suggests that PTSD can influence schizophrenia symptoms. This is illustrated by the increase of more positive symptoms of schizophrenia and more general psychopathology associated with PTSD in individuals with schizophrenia (Sautter et al., 1999). In the interactive model proposed by Mueser et al., PTSD can directly and indirectly affect symptom severity, risk of relapse and use of services. “Direct pathways could be avoidance of trauma related stimuli, distress related to re-experiencing the trauma, and overarousal” (Mueser et al., 2002). For example, Mueser et al. (2002) cite that the avoidance of trauma related stimuli and distress related to re-experiencing the trauma in PTSD could result in increased social isolation for individuals with schizophrenia and increased vulnerability to psychotic symptoms. Indirect influences include things like difficulty in relationships or an increased likelihood of utilizing substances, which would increase the risk of experiencing a traumatic event. For a graphic description of the interactive model see Figure 2. Individuals with schizophrenia or PTSD may have difficulty interacting with and understanding their environment, they may not be as cautious because they have a foreshortened sense of the future, are utilizing substances, or do not possess the safety of a shelter (i.e., homeless). They may also be so focused on specific triggers or avoidance of those triggers that they miss other important cues in their environment making them more susceptible to trauma (Mueser, Rosenberg, Goodman, & Trumbetta, 2002). Furthermore, people with severe mental illness have less coping resources to deal with the effects of trauma (Seedat et al., 2003).

Neurocognitive Deficits in Comorbid Schizophrenia and PTSD. Despite the accumulating evidence for neurobiological dysfunction in both schizophrenia and PTSD, there is a dearth of studies specifically examining the nature and severity of brain structure and function abnormalities in those individuals with these comorbid diagnoses. One study conducted by Lysaker, Meyer, Evans, & Marks (2001) examined neurocognitive impairment associated with a childhood history of sexual abuse in individuals with schizophrenia. This study identified deficits in working memory and information processing, suggesting that neurocognitive deficits are likely found in the comorbid presentation of schizophrenia and PTSD and that these deficits would be more than those associated with purely a history of childhood sexual abuse.

Figure 2: Interactive model of trauma, PTSD, and severe mental illness. PTSD is hypothesized to worsen the severity and course of serious mental illness through the direct effects of PTSD symptoms and indirectly through the effect of PTSD on substance abuse, retraumatization, and a poor working alliance with clinicians, leading to receipt of fewer preventative illness management services. Reprinted from Mueser et al. (2002).



There are other non-specific studies suggesting that extreme stressors may provide a viable mechanism for neural damage in patients diagnosed with schizophrenia. For example, Walker and Diforio (1997) suggested that a smaller hippocampus in first-episode schizophrenia could also be related to prior exposure to stress. They found that individuals with schizophrenia had elevated cortisol at baseline and after pharmacological challenges, suggesting that individuals with schizophrenia had been previously been exposed to stressful situations. More recently, Corcoran et al. (2003) have suggested that because “.....the biological effects of stress are mediated by the hypothalamic-pituitary-adrenal (HPA) axis, which governs the release of steroids, including cortisol.... the HPA axis and its interaction with intervening life events are apt candidates for study” (p. 671). Thus, the exploration of brain function in those with comorbid PTSD is an important area of investigation.

As previously suggested, both schizophrenia and PTSD are associated with unique patterns of neurocognitive deficits. Those suggesting that there is a single etiology for both PTSD and schizophrenia state that both disorders have the same physiological attributes and subsequent neurocognitive deficits. In addition, this model suggests that the neurocognitive deficits are present by the first-episode of schizophrenia, providing some evidence to suggest that the neurocognitive deficits associated with schizophrenia could potentially have been caused by a traumatic event. Walker and DiForio (1997) provide some evidence for pre-existing HPA hyperactivation in individuals with schizophrenia. Walker and DiForio found that individuals with schizophrenia already had a negative response to dexamethasone suppression test (DST) suggesting prior exposure to traumatic events. However, a close examination of the

literature does not provide strong support for the idea that the same pattern of neurobiological and neurocognitive dysfunction exists in both in schizophrenia and PTSD. Specific areas of improper function common to both disorders include hyper-reactivity of the hypothalamic-pituitary-adrenal axis (HPA), improper function of neurotransmitters, and hippocampal volume and function (Seedat et al., 2003). Contrary to this model, however, is evidence to suggest that schizophrenia does have some unique impairments not seen in PTSD (e.g., motor function and smell deficits).

To arrive at a prediction regarding the neurocognitive performance associated with comorbid schizophrenia and PTSD, the results of the neurocognitive findings for each disorder will be summarized. In schizophrenia, there have been consistent deficits across all domains of neurocognitive function. In PTSD, research has been more inconsistent with regard to the corresponding neurocognitive function. There is some support for the idea that attention, executive function, working memory, and verbal memory are slightly impaired.

The resulting predictions regarding the neurocognitive of the comorbid group are a combination of the effects for each group, with some multiplicative effect of impairment for each domain. Therefore, it may be predicted that the comorbid group will not have any additional deficits than those occurring in schizophrenia alone on motor function. A synergistic effect would also not be predicted in regards to visual memory as there is not literature to suggest these impairments in PTSD. On the other hand, both groups individually have been associated with impairments across the remainder of the domains and so it would be predicted that the comorbid group will exhibit a level of impairment more severe than the impairment associated with either disorder alone, and

impairment more severe than reflecting the addition of the corresponding deficits for each group, supporting a synergistic model.

However, because no studies have examined the neurocognitive deficits associated with comorbid schizophrenia and PTSD, the pattern of deficits suggested for those with schizophrenia PTSD comorbidity remains speculative. Furthermore, the models previously reviewed that have attempted to explain the high prevalence of schizophrenia PTSD comorbidity do not have direct application to neurobiological dysfunction, and so provide little guidance in generating hypotheses in this area. As the current models explaining high schizophrenia and PTSD comorbidity do not consider the interacting effects of neurocognitive function, three alternative models are proposed.

The first model postulates that the etiology of PTSD and schizophrenia are the same so there would be no unique deficits to either disorder, they would only vary in severity. The other two models, the additive model and the synergistic model, suggest that the etiology of PTSD and schizophrenia are different. The additive model suggests that there will be some unique deficits associated with each disorder and that individuals with comorbid PTSD and schizophrenia will perform more poorly than those with either PTSD or schizophrenia alone. In fact, the performance deficit associated with comorbid PTSD and schizophrenia would be a pooled total (sum) of the deficit associated with PTSD and schizophrenia. While the final model, the synergistic model, also assumes different etiology of the two disorders, it asserts that the total deficits associated with comorbid PTSD and schizophrenia are not just the combined total of the deficits associated with either disorder. Rather, the total deficits in schizophrenia PTSD comorbidity are multiplicative or synergistic. This study will evaluate these models by

comparing the pattern and extent of neuropsychological deficits associated with each disorder separately and when the disorders are comorbid.

The additive and synergistic models pre-suppose that schizophrenia and PTSD have different etiologies. Additionally, it would be suggested that the physiological processes underlying each disorder might contribute to the neurocognitive effects of the comorbid presentation. In particular, research has cited that noradrenergic and corticotrophin-releasing hormone systems in PTSD can augment the stress response and contribute to schizophrenia (Seedat et al., 2003). Conversely, long-term antipsychotic usage associated with schizophrenia can cause dopaminergic hypofunction, decreasing the firing rate in the locus coreleus and enhancing the noradrenergic activity seen in PTSD (Seedat et al., 2003). These are only two possible explanations of the complex interaction of how the physiological process associated with each disorder may interact to create increased cognitive impairment.

Hypotheses

The main purpose of this study was to determine the neurocognitive profile of comorbid schizophrenia and PTSD. The results of this study can further clarify whether PTSD and schizophrenia have the same underlying etiology or different etiologies, while at the same time providing support for a model to demonstrate if and how the two disorders influence one another. The answers to these questions will be important in both the treatment and prevention of PTSD and comorbid schizophrenia. Currently, trauma history and PTSD are largely ignored in treating individuals with schizophrenia. Also, psychological and pharmacological treatment for schizophrenia and PTSD vary

considerably suggesting that proper treatment of comorbid PTSD can potentially mitigate many of the serious adverse effects seen in schizophrenia.

To answer these questions a four-group design was used: controls (C), a group of individuals with PTSD (PTSD), a group of individuals with schizophrenia (SZ), and individuals that have comorbid schizophrenia and PTSD (SZP). All groups were tested on a comprehensive neuropsychological battery, which assessed all cognitive domains. Comprehensive interviews were also conducted to evaluate psychiatric symptoms and diagnoses.

- I. On schizophrenia symptom measures (SANS, SAPS, and BPRS) the SZ groups will score significantly higher than the PTSD group. In regard to the SZ and SZP groups, it is predicted that the SZP group will score higher on the SAPS, the measure of positive symptoms of schizophrenia, and the BPRS, a measure of more general psychiatric symptoms. It is predicted that the SZ group will score higher on the SANS, a measure of negative symptoms. It is hypothesized that the two groups with PTSD will score higher than the SZ control group on other symptom measures (CDS and PCL).
- II. On the motor domain measures, there should be no difference between the SZ and SZP groups. Additionally, the PTSD and Control groups will score significantly higher or exhibit no impairment.
- III. For this hypothesis it was predicted that:
 1. On measures of neurocognitive impairment including explicit memory (verbal and spatial), working memory (verbal and spatial), emotional

memory, executive function and attention, all three clinical groups would exhibit impaired performance relative to controls.

2. The comorbid group would have significantly more impairment than either the PTSD or SZ group.
 3. The level of impairment is more than the deficits associated with either schizophrenia or PTSD combined supporting a synergistic model of neurocognitive deficits.
- IV. The SZ and SZP group will have significantly lower scores on the WAIS-III subscales: Information, Vocabulary and Block Design.

CHAPTER 3

METHODOLOGY

Participants

The participants in the study were recruited from the community and the University of Nevada, Las Vegas. For the most part, the individuals with schizophrenia were clients at Mojave Mental Health, a day treatment program for individuals with severe mental illnesses, controls were obtained from the community, and PTSD participants were recruited from the psychology subject pool. Each group had some participants who were recruited through one of the other methods (i.e., some Control participants recruited from the community were included in the PTSD group). The Control group had 26 participants. The PTSD group had 21 participants. The SZ control group had 26 participants and the SZP group had 21 participants. These numbers reflect fewer participants than completed the study in order to more closely match the groups on age and education. Participants ranged between 18 and 60 years old.

Participants were compensated for participation monetarily or with credits to fulfill the undergraduate research requirement. Undergraduate students received one credit for each hour of their participation, with a minimum of five credits. Participants from the community received \$5 per hour with a \$30 bonus for completing the study. For the undergraduate students who were not able to continue in the study based on eligibility requirements they were still given the five research credits. This was based on

the fact that the student had committed to a five hour block of time when signing up for the study. Participant payments were somewhat variable and ranged from \$60 to \$100 dollars. The reason for this variability was based on the amount of time it took for the individual to complete the testing. There was a great deal of variability in the length of time necessary to complete the tests based on the number of breaks necessary, the actual response time for individual items, and in the length of the structured interview.

Participants from the community who were unable to participate based on eligibility requirements were paid for the time they had spent with the interviewer. This was between \$2.50 and \$10.00 with the majority of the people receiving \$2.50. Testing took between four and ten hours based on the individual factors mentioned above and was completed in as many sessions as necessary based on the needs of the participant.

All participants gave informed consent prior to participating in the study.

Exclusionary criteria applicable to all of the groups included a history of a head injury, seizures, mental retardation, if English was not their primary language or they were unable to provide consent. Individuals were included in the Control group if they did not have any psychiatric diagnoses as determined by the Structured Clinical Interview for DSM-IV (SCID). However, participants were included in the Control group if they had a discrete psychiatric episode that had resolved more than one year ago (e.g., depression). Participants were also excluded from the Control group if they had been exposed to a traumatic event and experienced subthreshold symptoms of PTSD.

Participants could only be included in the PTSD group if they had a lifetime diagnosis of PTSD as determined by the SCID. For the SZ group, individuals with a diagnosis of schizophrenia as assessed by the SCID and confirmed with medical records

and they did not have subthreshold levels of PTSD. Individuals in the comorbid schizophrenia PTSD group had a diagnosis of both schizophrenia and a lifetime diagnosis of PTSD. Individuals could not have a current substance dependence diagnosis in any of the three clinical groups. Individuals in the three clinical groups were not excluded on the basis of other psychiatric disturbances. Other psychiatric symptoms were not an exclusion from any of the three clinical groups. This more accurately reflected the general population of those individuals with schizophrenia and PTSD. Additionally, it was expected that random assignment to either one of the schizophrenia groups would factor out the effects of other symptoms.

Procedure

Participants were recruited through an advertisement in the psychology subject pool, after a brief description provided by one of their mental health workers or by one of the researchers for the study. Individuals who were interested in participating in the current study provided written informed consent prior to completion of any of the study procedures. Appendix I contains the four informed consent forms used in the study. There was an informed consent form for the Control participants recruited from the community, for the Control participants recruited from the psychology subject pool, for the PTSD participants recruited from the psychology subject pool, and the schizophrenia subjects recruited from the community. Study procedures were usually completed over multiple sessions, however, many of the PTSD participants required only one session because the total assessment time for this group was usually 4 hours. The demographic and symptom measures were always given first to determine eligibility for the study. Control subjects were not given the clinical interview to determine SANS, SAPS, CDS or

BPRS scores based on the fact that these assessments are designed for individuals with clinical populations.

Neuropsychological testing and self-report measures were administered as the second component in the study. The neuropsychological tests were administered in a random fashion. This was done for a variety of reasons. The first priority was to accommodate the needs and comfort of the participants. For example, sometimes the participant would need to switch the type of tasks they were doing in order to improve concentration or decrease frustration. At other times, the participant would need to leave at a specific time limiting the type of task to be completed in that time frame. At other times, there were constraints on the situation. For example, testing was concurrently occurring in three different locations by multiple examiners and certain materials were only available in specific rooms. Finally, random administration of the tests controlled for potential carryover or practice effects. Practice effects were of particular importance on the memory measures. The CVLT, EVLT and Biber all had the same administration format and so following exposure to the first memory test, performance could have potentially been facilitated on subsequent memory tests. There were some exceptions to the randomization of neuropsychological tests. During the intervals for each of the memory tasks, individuals were not given any other memory task. Furthermore, individuals could not be given a task during an interval for a memory test that was within the same modality (e.g., Block Design could not be administered in the delay of the Biber Figure Learning Test). Detailed descriptions of all tests and testing procedures are provided in the measures section. Furthermore, in the measures section, the tests will be grouped to illustrate how the cognitive domains were identified. Each test was

administered according to standardized instructions. Psychometric data of all tests are available in standard neuropsychological tests (Lezak, 1995; Spreen & Strauss, 1998) or are provided in the following section if not readily available.

All testing was conducted by the primary author or other trained graduate students, and occurred in a quiet setting (office). There was time for questions at the conclusion of the examination, and the participant was given a debriefing form containing experimenter contact information and information regarding the nature of the study.

Measures

A demographic questionnaire was given to all participants (see Appendix II). The remainder of the measures represented standardized instruments used to arrive at clinical diagnoses, assess clinical symptoms, or to assess neuropsychological function. After the participants completed the demographic questionnaire, participants were interviewed to assess psychiatric symptoms. Inclusion and exclusion criteria based on these measures are described above in the participants section. The neurocognitive tests were administered following the screening and symptom rating scales. Each of the measures utilized in this investigation are described in the following section. All of the neuropsychological tests, as well as the clinician-administered rating scales and the structural clinical interview, are commonly used tests that have been found to be valid and reliable for research purposes.

Screening and Symptom Measures

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)

The Structured Clinical Interview for DSM-IV Axis I Disorders- (SCID-I for DSM-IV (SCID-DSM-IV; First, Gibbon, Spitzer, & Williams, 1996) is a semi-structured interview developed for obtaining DSM-IV Axis I diagnoses. It is administered by individuals trained in the DSM-IV diagnostic system (APA, 1994) and is utilized with both psychiatric and general medical patients, as well as, with individuals in the community for the purpose of mental health surveys and research. All of the standard modules were administered, with the exception of the specific phobia and eating disorders sections. Scoring or rating of the SCID modules involves rating each response to the diagnostic criteria either as 1 (symptom is absent), 2 (subthreshold symptom) or 3 (symptom is present). Diagnosis of an Axis I disorder is based on the DSM-IV. A rating of three is endorsement of the symptom. Kappa values range from .02 to .98 with the majority of the values ranging from .4 to 1. There is a very low rate of false negatives. A study conducted by Fennig et al. (1994) suggests that the SCID is a valid instrument for the diagnosis of schizophrenia, as SCID schizophrenia diagnoses displayed good sensitivity (.89), specificity (.96), and agreement (.86) when compared to best estimate diagnosis made by psychiatrists on first-admission psychotic patients.

PTSD Checklist-Civilian (PCL-C).

On the PCL-C (Weathers, Litz, Herman, Juska & Keane, 1993), participants are asked to rate how often they experience the 17 symptoms characteristics of PTSD within the last month. The potential answers are in a Likert scale format with “1” representing “Not at all” and “5” representing “Quite a Bit”. In this version of the PCL, questions are

written generically so they could apply to any traumatic event. This questionnaire can be used for diagnosis in two different ways. The items can be added to receive a total score and then a specified cut-off will indicate the presence of PTSD (30 is the recommended low cut-off). Another option is to utilize the scale, following the criteria of diagnosis for PTSD set forth by the DSM-IV. The questions on the PCL can be broken down into the three clusters described in the DSM-IV: persistent re-experiencing, persistent avoidance of trauma related stimuli and numbing, and hyperarousal symptoms. A score of three or more is considered endorsement of the symptom. There must be at least 1 re-experiencing symptom, 3 avoidance items, and 2 symptoms of increased arousal. Criteria must be met for all three clusters of symptoms. This study utilized the latter method for diagnosis and total scores in statistical analyses. Test-retest reliability is .96 and item scale total correlations range from .62-.87. There is high convergent validity with other scales like the Mississippi Combat Scale (.93), and the PCL-C has similar sensitivity (.82) and specificity (.83) to the SCID. This measure has also been used in populations with severe mental illness.

Brief Psychiatric Rating Scale (Overall, Gorham, 1962; BPRS).

The BPRS consists of 18 items designed to assess 18 constructs representing various psychiatric symptoms. It is administered in a semi-structured interview format. Each item is evaluated on a 7 point Likert scale with “1” representing “not present” and “7” representing “very severe”. The Brief Psychiatric Rating Scale (BPRS) is commonly employed in the assessment of clinical symptoms associated with schizophrenia and other psychiatric disorders. Symptoms are rated both by subjective and objective reports. The BPRS interview was conducted at the same time as the SCID for the clinical groups.

The Calgary Depression Rating Scale (Addington, Addington, and Schissel, 1990; CDS).

The CDS is a nine item scale specifically developed to assess depressive symptoms in individuals with schizophrenia. The items are rated on a Likert scale format on a four point scale with “0” representing “never” and a “3” representing “severe”. Items are rated from the patient’s responses to questions in an interview format and the last item is a subjective response from the interviewer. The items are designed to be more representative of the depressive symptoms experienced by individuals with schizophrenia that are not influenced by antipsychotic medication. The scale has an internal consistency of .76.

Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984).

The SAPS is designed to assess the positive symptoms associated with schizophrenia. The scale is a complementary scale to be used with the SAPS. A structured clinical interview draws on direct observations of behavior and subjective reports of behavior. The scale provides clear definitions of each one of the statements and a scaled anchor system. Several items measuring the same construct are then compiled into a global rating. The SAPS has the following global ratings: hallucinations, delusions, bizarre behavior, and positive formal thought disorder.

Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984).

The SANS is the complement to the SAPS designed to assess the negative symptoms associated with schizophrenia. Once again, a structured clinical interview is designed to obtain objective and subjective ratings of behavior. Behaviors are rated individually and then grouped into domains for a global rating. On the SANS the global

ratings are affect, alogia, avolition, anhedonia and attention. Before each category definitions are provided for each symptom. There are also behavioral anchors for each symptom.

Neuropsychological Test Battery Domains

Executive Function Domain

Trail Making Test - Part B. The Trail Making Test - Part B requires the examinee to connect numbers and letters in alternating order with speed and efficiency. For example, the examinee must connect the number 1, then the letter A, then the number 2, followed by the letter B and continuing in this fashion until the end of the test. Trails B is a measure of visuomotor processing speed and executive functioning, as it requires the ability to process items within a visual field and manually trace those items, while constantly shifting cognitive set. The score is obtained by calculating the total amount of time (in seconds) required for task completion. Psychometric properties of the Trail Making Test are detailed under the Trail Making Test- Part A section. If the participant had difficulty completing the task, The Trail Making Test Part B was discontinued after five minutes and the participant would receive a score of 301 seconds to indicate that they could not complete the test.

Wisconsin Card Sorting Test (WCST). In the Wisconsin Card Sorting Test, participants are asked to categorize test cards to one of four stimulus cards placed in front of them. The stimulus cards consist of a red triangle on the first card, two green stars on the second, three yellow crosses on the third, and four blue circles on the fourth card. The test cards consist of different geometric forms, which have a different shape, number, and color of stimuli. The subject is given one card at a time and asked to sort according

to an underlying principle, with no other instructions except that they would be given feedback regarding their performance. The categorization rule shifts after ten successful responses, unknowingly to the participant, and then the subject must shift their sorting rule accordingly. This test measures, among other concepts, abstract concept formation and the ability to shift cognitive sets as feedback is given. The WCST has been shown to be sensitive to dorsolateral prefrontal cortex (Sullivan, Mathalon, Zipursky, Kersteen-Tucker, Kight, et al., 1993). The dependent measures used in this test are the percentage of perseverative errors and the number of categories completed.

Controlled Oral Word Association Test (COWAT). The Controlled Oral Word Association Test is a measure of verbal fluency. Participants are asked to generate as many words as possible beginning with a given letter (phonetic fluency) or a specific category (semantic fluency) within a 60 second time period. The most commonly used letters are F, A, and S, which were the letters used in this study. Proper names are not allowed nor are the same words with different endings or suffixes. The second portion of the COWAT involves category or semantic association in which a participant is asked to generate as many items of a particular category within 60 seconds, with the most common categories including animals, things in the kitchen, things to wear, etc. The semantic category of animals was used in this study. The semantic category fluency test has been shown to activate primarily right dorsolateral and medial frontal region (Cardebat et al., 1996), whereas the letter fluency category has been found to be more sensitive to left frontal and temporal regions (Loring et al., 1994). The score used is the total number of words minus intrusion errors and perseverative responses.

Attention Domain.

Stroop- Color/Word Association Test (Stroop, 1935; Golden, 1978). The Stroop was administered by computer. The participant was asked to identify the color of words as quickly as possible. The participant was first given a practice trial to learn the task. The practice trial began by teaching the participant how to name the color of the word. The color name and the color that the word was printed on are congruent. After several trials, the stimuli may be printed in one color, but the word is another color. For example, the word may say red, but be printed in the color blue. The correct response would be “blue”. These trials are considered the interference trials and represent the ability to suppress the undesired response. The trials are administered in a random sequence, with some trials printed in matching colors and words (congruent) and others that are incongruent (words are printed in a different color than they read). The dependent variable in this study was the accuracy of the response.

Trail Making Test – Part A. The Trail Making Test is a measure of attention, which also contains a motor component (Lezak, 2004). It has proven sensitive to detecting cognitive impairment resulting from brain related abnormalities in numerous clinical populations, including schizophrenia (Crockett et al., 1988). The test contains 2 parts, Part A and Part B. Part A is primarily considered a measure of attention, whereas Part B is more frequently considered a measure of executive function. Part A consists of 25 numbers in which the examinee is required to connect in sequence of ascending order under timed conditions. The subject is instructed to connect the circles as quickly as possible, without lifting the pencil from the paper. Performance on part A is measured by calculating the amount of time (seconds) required to connect all the numbers in the

appropriate sequence. Reliability estimates reported for the Trail Making Test have been variable, with r values ranging from .36 to .94; however the majority of reliability scores exceed .60 (Spreen & Strauss, 1998).

Motor Function

The Finger Tapping Test. The Finger tapping test is an index of psychomotor speed and control, which is used to detect subtle motor and cognitive impairment (Spreen & Strauss, 1998). In the Finger Tapping Test, participants are instructed to use the index finger of their preferred hand to tap a lever as rapidly as possible for a total of five consecutive 10-second trials. Examinees are restricted to using the index finger only, refraining from moving any other fingers. A break is generally provided after the third trial. Procedures are then repeated using the non-dominant hand for five trials. A final Finger Tapping score is obtained for dominant and nondominant hands by averaging the number of taps obtained on the five trials. Additional trials are administered upon the occurrence of a variation of more than 5 taps from the highest to the lowest trial. This is done to obtain an accurate estimate of performance. In instances where examinee performance varied by greater than 5 taps within the 5 trials, a maximum of ten trials were administered, and the final tapping score is obtained by averaging scores of five trials within the range of five taps or less.

Purdue Pegboard. The Purdue Pegboard measures gross movement of arms and hands, along with fine movement dexterity. Tiny silver rods are placed into holes in a board. The dependent measure of the test is the number of pegs placed within 30 seconds. There is a trial for the dominant hand, the non-dominant hand and both hands together. The test-retest reliability ranges from .85 to .90.

Working Memory

Digit Span Forward from the WMS-III. On the Digit Span Forward participants are read a series of numbers and asked to repeat them verbatim. The sequences start at a series of 2 numbers and increase by one number every two trials until the participant performs two consecutive trials of the same sequence length incorrectly.

Digit Span Backward from the WMS-III. On the Digit Span Backward the participant is read a series of numbers and asked to repeat them backwards. The sequences start at 2 numbers and increase by one number every two trials until the participant performs two consecutive trials of the same length incorrectly. The total number of correct trials can be summed for both digits forward and backward for a total score.

Spatial Span Forward from the WMS-III. The Spatial Span Forward is the visual analog of the Digit Span subtest. The Spatial Span Forward measures an individual's ability to hold a sequence of blocks tapped on a board in working memory and to then reproduce the sequence. The board is three-dimensional with ten blue blocks protruding. The examiner taps out a fixed sequence of patterns at a rate of 1 block/second.

Spatial Span Backward from the WMS-III. The Spatial Span Backward test uses the same apparatus as the Spatial Span Forward. The examiner once again taps out a design on the blocks. This time, the participant must hold the design in memory and then repeat the design backwards.

Explicit Memory

Verbal Memory—California Verbal Learning Test II (CVLT; Delis, Kramer, Kaplan, & Ober, 1987). The CVLT was used as a measure of declarative verbal learning

and memory. The word lists are presented over five trials. The words on this list include sixteen commonly used shopping items (List A), representing various categories such as spices, tools, fruits, and clothes. Words are presented at the rate of one per second, and the participant is asked to recall as many words from List A following each presentation of the list. After five trials, a second list (List B) is introduced as a distractor list, and the participant is asked to recall as many items as they can from this second list. After recalling the words from the second list, the participant is asked to recall and repeat the words from the first list again without the list being repeated. Following the short-delay recall trial, the participants are cued with the categories of fruit, clothing, tools, and spices (Cued recall) and are again asked to recall as many items as possible in each category. Following a 20-minute delay in which non-verbal tasks are performed, the participants are asked to recall as many items from list A in both a free recall and cued situation. The final component of the test is recognition of stimulus words. The trial includes a listing of words with some words from the first list, some words from the second list, and some words that were not included in the test. The participant is instructed to answer “yes” if the word was on the first list and “no” if the word was not on the first list. Therefore, the CVLT measures recall, recognition and list learning; interference effects and retrieval/encoding difficulties can also be evaluated with this measure. The dependent variables to be used in this study were the total number of words recalled on trials one through five, the number of words recalled on list B, the short-delay number of words recalled, the number of words recalled on the long-delay and the number correct on the recognition trial.

Visual Memory—Biber Figure Learning Test-Extended (BFLT-E; Glosser et al., 1997). The BFLT-E will be used as a measure of visual or non-verbal learning and memory. The BFLT-E has been described as the visual analog of the California Verbal Learning Test (Kurtzman, 1996; Traci, Mattson, King, Bundick, Celenza, & Glosser, 2001; Glosser, Cole, Khatri, DellaPietra, & Kaplan, 2002), such that both tests involve a series of five learning trials, an interference task, as well as, an immediate recall, delayed recall condition, and a recognition trial. The BFLT-E, a modification of the original Biber Figure Learning Test, (BFLT; Glosser et al., 1989), and consists of 15 geometric designs constructed of simple shapes (circles, squares, and triangles) put together to form novel stimuli. The fifteen designs are presented one at a time at a rate of one every 3 seconds. Following presentation of the designs, the participant is asked to draw as many of the figures as he/she can recall in no particular order. This is done for five trials. Then similar to the CVLT, an interference task is introduced with distractor figures followed by an immediate free recall trial of the original list. A delayed learning recall trial is administered 20 to 30 minutes later, with verbal (non-visuospatial) tasks conducted in the delay. A recognition trial asks the participant to identify the designs from the first list. The Biber Figure Learning Test is scored on a scale of zero to three for each stimuli. Although the CVLT and the BFLT-E are not identically matched in terms of difficulty level and item content, they can serve as relative measures of verbal and non-verbal learning (Tracy et al., 2001). The inter-tester reliability has been found to be .98. (Glosser et al., 2002). The BLFT-E has also been shown to have good test-retest reliability and criterion validity (Glosser et al., 2002) and to demonstrate sensitivity to non language-dominant right temporal lobe functioning.

Emotional Memory—Emotional Verbal Learning Test (EVLT; Strauss & Allen, unpublished manuscript). The EVLT is a measure of learning and memory for emotional words. All procedures, parameters, and score calculations are modeled after the CVLT-II (Delis, 2000), allowing for a direct comparison between learning and memory performance for emotional and neutral words. The EVLT is a standardized measure with psychometric properties comparable to the CVLT-II (internal consistency, $r = .88$).

The task first requires the experimenter to orally present 16 words (List A) over five immediate-recall trials. The list consists of 4 words from each of four “basic emotion” categories (Happiness, Sadness, Anger, and Anxiety). Individual words of the same category are never presented successively to allow for the assessment of semantic clustering. Following the 5 immediate recall presentations, a second “interference” list (List B) is presented for a single trial. Immediately following List B, a short delay free and category cued recall of List A is administered. A 20-minute delay then occurs between the presentation of the short-delay and long-delay free recall assessments. Long delay free and cued recall is then assessed. Recognition of List A is measured using a yes-no recognition format immediately following the administration of the long delayed recall. In the test of recognition, there are 28 distractors consisting of: List B emotional words semantically related to List A words, List B emotional words semantically unrelated to List A words (disgust words), novel words that are prototypical of semantic categories presented in list A, and emotional words semantically unrelated to List A words (fear and surprise words). Normative data collected on the EVLT suggest that psychologically healthy individuals evidence a memory bias for happiness words (Strauss

& Allen, unpublished manuscript). This memory bias is not accounted for by list order, word frequency, word length, or emotional prototypicality.

Estimates of Intelligence Function.

The following three tests are subtests from the WAIS-III, the Wechsler Adult Intelligence Scale 3rd edition (Wechsler, 1997).

Block Design. On the Block Design subtest individuals are asked to make a series of designs utilizing blocks. The blocks each have one red side, one white side, and two sides that are half-red and half-white. The designs begin with a pattern utilizing only four blocks and get progressively more difficult to designs necessitating nine blocks. Designs must be administered in discrete amounts of time. Responses are scored for accuracy and time to complete. The administration of this subtest is discontinued after three trials that are not completed correctly.

Information. On the Information subtest, the participant is asked to answer several questions. Questions represent a general fund of knowledge from multiple content areas including geography, history, science, etc. Answers receive one point for a correct answer. The subtest is discontinued after six consecutive incorrect trials.

Vocabulary. On the Vocabulary subtest, participants are asked to give definitions to increasingly difficult words. Responses may be given up to two points and may receive partial credit.

CHAPTER 4

RESULTS

Preliminary Analyses

The raw data were examined to detect any out-of-range variables. All of the variables were then checked to determine if they were normally distributed. Some variables exceeded acceptable limits for skewness and kurtosis. These included the Trail Making Test part A, the Stroop total scores, and the recognition scores on the CVLT and Biber Figure Learning Test.

Although multivariate analysis of variance (MANOVA) has been found to be relatively robust with respect to violations in assumptions of normality and homogeneity (Tabachnick & Fidel, 2001), the variables identified above were converted to ranked scores and then entered in parametric analyses, to ensure that the variables were not being overly influenced by non-normal distributions. The parametric analyses were conducted first followed by the method described above to correct for non-normality. Both parametric and nonparametric results will be discussed in the corresponding sections.

Following inspection of the data, preliminary analyses were conducted to examine demographic differences among the groups. For these analyses, one-way analyses of variance (ANOVA) were used for age and education, and chi-square analyses were used for categorical variables (ethnicity, sex, gender). The results of these analyses as well as the descriptive data for each group are presented in Table 1. The ANOVA for age was

significant, with post-hoc analyses indicating that the PTSD group was significantly younger than the Controls and schizophrenia groups. On the other hand, the Control, SZ, and SZP groups did not significantly differ from one another. The ANOVA for education was also significant, although post-hoc analyses did not reveal any significant differences between any of the groups. The ethnicity of the groups was compared using a chi-square analysis. The results of the test were not significant, $\chi^2(21, N = 92) = 29.07$, $p = .10$. The chi-square for gender was significant $\chi^2(3, N = 90) = 10.24$, $p = .02$. Consistent with prior studies investigating the percentage of trauma in individuals with schizophrenia, 76% of the individuals with schizophrenia had been exposed to a traumatic event.

Evaluation of Study Hypotheses/Main Analyses

Following the preliminary analyses, MANOVA was utilized to evaluate the study hypotheses. The first hypothesis regarded differences in psychiatric symptoms among the groups, while the remaining three were concerned with differences in neuropsychological function. Tables 1-17 contain descriptive statistics as well as the results of the statistical analyses and post hoc (Scheffé) tests for all eight neuropsychological domains. Composite scores were derived by summing and averaging the z-scores of the measures in a particular domain. To calculate z-scores, the means and standard deviations of the raw scores from the normative sample were used. Figure 4 demonstrates the pattern of neurocognitive performance across domains by group.

Hypothesis One:

On schizophrenia symptom measures (SANS, SAPS, and BPRS) the SZ groups will score significantly higher than the PTSD group. In regard to the SZ and SZP groups, it is predicted that the SZP group will score higher on the SAPS, the measure of positive symptoms of schizophrenia, and that the SZ group will score higher on the SANS, a measure of negative symptoms, and the BPRS, a measure of more global psychiatric symptoms. It is hypothesized that the two groups with PTSD will score higher than the SZ control group on other symptom measures (CDS and PCL).

Separate MANOVA's were used to compare the groups on clinical symptoms as assessed by the SANS and SAPS, and ANOVA's were used to compare the groups on the BPRS Total Score, the Calgary Depression scale and the PCL Total Score. The statistics for the symptom ratings for the three clinical groups are presented in Table 2 with the corresponding values for the statistical analyses. For the SANS, the overall MANOVA was significant $F(10,122) = 6.54, p < .001$, with the SZ group scoring higher than the SZP group on the SANS subscales. Because the MANOVA was significant, subscale ratings were accomplished to evaluate if there was a differential pattern of symptoms within the measures. The PTSD group scored significantly lower than the SZ groups on all of the subscale scores. Scheffe post-hoc analyses indicated that all three groups were significantly different from one another on the affective flattening subscale score with the SZ group having the highest score and the PTSD group with the lowest score. On the alogia, avolition-apathy, anhedonia-asociality, and attention subscales the SZ and SZP groups did not differ significantly from one another, but were significantly different from the PTSD group. For the SAPS, the overall MANOVA was also significant $F(8,124) =$

15.46, $p < .001$. The pattern of symptoms on the SAPS was different than what was seen on the SANS, with the SZP group scoring higher than the SZ group on some of the SAPS subscales. The SZP group scored higher than the SZ group on the hallucinations and delusions subscales indicating more severe symptoms in the SZP group. The SZ and SZP groups scored significantly higher than the PTSD group. Conversely, on the bizarre behavior and thought disorder subscales the SZP group scored lower than the SZ group. The SZP and PTSD groups were not significantly different on these two ratings.

Separate ANOVA's revealed significant differences on the CDS, BPRS and the PCL. On the CDS the SZ group scored significantly lower than the PTSD group and the SZP group, indicating more depressive symptoms in the PTSD and SZP groups. All three groups differed on their PCL scores with the SZ group scoring the lowest followed by the PTSD group. The SZP group received the highest scores on the PCL, indicating the highest level of PTSD related symptoms. On the BPRS the PTSD had significantly lower symptoms than the SZ and SZP groups and the SZP group had higher symptom scores than the SZ group, once again, indicative of increased levels of overall psychiatric symptoms.

Hypothesis Two:

On the motor domain measures, there should be no difference between the SZ and SZP groups. Additionally, the PTSD and Control groups will score significantly higher or exhibit no impairment in comparison to the SZ and SZP groups.

Descriptive statistics and MANOVA results for motor functioning are presented in Table 3. As depicted in the table, the overall MANOVA was significant $F(15,258) =$

2.78, $p < .001$. All univariate tests were also significant. Scheffe post-hoc analyses indicated that on all of the measures, the Controls and PTSD groups had the best performance. On pegboard scores, Scheffe post-hoc analyses indicated that the SZP group was not significantly different than the other three groups.

Because of the known associations between neuropsychological test performance and variables such as age, education and positive and negative symptoms, the impact of these variables on the motor differences among the groups was examined using a series of covariate analyses. In the first of these analyses, effects of age and education were examined by including age and education as covariates in a MANCOVA. The results of these analyses indicated that age was not a significant covariate, $F(5,82) = .72, p = .61$, nor was education, $F(5,82) = 1.11, p = .36$. Furthermore, the overall effect for groups remained significant, $F(15,252) = 2.38, p = .01$. Inspection of the means for the individual test scores after covarying out the effects of age and education further suggested that while there were some minor changes in values, the overall pattern of differences among the groups remained the same. See Table 9 for comparison of the descriptive statistics corrected for age and education.

Similar analyses were then accomplished for symptoms variables, specifically the SANS and SAPS total scores and the PCL total score, as there were also significant differences among the groups on these variables. The results of these analyses indicated that the SANS was not a significant covariate, $F(5,80) = .14, p = .98$, nor was the SAPS, $F(5,80) = .23, p = .95$, or the PCL, $F(5,80) = .102, p = .41$. Although none of the symptom measures were significant, the overall effect for group was no longer significant in the MANCOVA $F(15,246) = 1.27, p = .22$. Inspection of adjusted means revealed

little effect of the covariates on raw motor scores. Thus, the lack of an overall difference may have resulted from decreased power with the inclusion of covariates.

Hypothesis Three:

For this hypothesis it was predicted that:

1. On measures of neurocognitive impairment including explicit memory (verbal and spatial), working memory (verbal and spatial), emotional memory, executive function and attention, all three clinical groups would exhibit impaired performance relative to Controls.
2. The comorbid group would have significantly more impairment than either the PTSD or SZ group.
3. The level of impairment would be more than the deficits associated with either schizophrenia or PTSD combined supporting a synergistic model of neurocognitive deficits.

Results of the separate MANOVA's, one for each of the six neurocognitive domains provided partial support for the first hypothesis. As can be seen in Tables 4 -7, these MANOVA's revealed significant overall differences in the domains of Verbal Learning/Memory, Visuospatial Learning/Memory, Emotional Learning, Working Memory, Executive Functioning, and Attention. The pattern of differences among the groups generally indicated that the Control group performed significantly better than the SZ groups. The PTSD group was not, however, significantly different from the Control group on most tests. Additionally, the SZ and SZP groups were not statistically different from each other throughout. As predicted though, the SZ and SZP groups did exhibit a pattern of performance within domains suggesting that PTSD in individuals with

schizophrenia may influence neurocognitive symptoms. This pattern was however, contrary to the hypothesis, in that the SZP group tended to have better performance than the SZ group.

A MANOVA was used to compare the groups on measures of memory. See Table 4 for descriptive statistics and statistical analyses. Separate MANOVA's were conducted for each of the memory domains. Verbal Learning and Memory was assessed with the CVLT. Visual Spatial Learning and Memory was assessed using the Biber Figure Learning Test and Emotional Learning was assessed with the EVLT. All of the aforementioned memory tests are similar to one another in that they have the same performance indices. All of the aforementioned memory tests included a total score for trials 1-5, a distractor trial, a short-delay trial, a long-delay trial and recognition section.

Verbal Learning/Memory

The overall MANOVA was significant for the CVLT, $F(21,252) = 3.66$, $p < .001$. Of the specific trials, univariate statistics revealed that all of the variables with the exception of the recognition section were significant. Results of univariate F tests are presented in Table 4. Scheffe post-hoc analyses indicated that the Control and PTSD group were significantly different from the SZ and SZP groups. There were no differences between the Control and PTSD groups or between the SZ and SZP groups. While the results were not significant, the SZP group consistently scored higher than the SZ group, whereas there was no consistent pattern between the Control and PTSD group.

Once again, a series of MANCOVA's were performed to evaluate the effects of age, education, and psychiatric symptoms on the verbal learning scores. The univariate analysis for age was not significant $F(4,83) = 1.14$, $p = .36$ and the univariate analysis for

education was not significant $F(4,83) = .69, p = .60$, although the effect for group remained significant $F(12,255) = 5.00, p < .001$. Similar analyses were then accomplished for the symptom variables. The results of these analyses indicated that the SANS was a significant covariate, $F(4,81) = 3.02, p < .05$. On the other hand, neither the SAPS, $F(4,81) = .91, p = .46$, or the PCL, $F(4,81) = .71, p = .58$ were significant. Since the SANS was the only covariate exerting an effect upon the variables, another MANCOVA was run with only the SAPS as a covariate, so as not to decrease power with variables that were not a significant influence. This MANCOVA was significant $F(5,57) = 2.15, p = .07$. The overall effect of group $F(10,116) = 2.90, p < .01$. Table 11 provides the corrected and uncorrected descriptive statistics for the Verbal Learning/Memory domain. Finally, the recognition scores were converted to ranked scores and compared with an ANOVA to better evaluate if the violations of normality influenced previous results from the parametric tests. The ANOVA for the ranked cases yielded the same results as the parametric analyses. The recognition scores remained non-significant, $F(2,91) = .87, p = .47$.

Visual Learning/Memory

A MANOVA was then used to compare the groups on visual spatial memory using the Biber Figure Learning Test. See Table 4 for descriptive statistics and statistical analyses. The overall MANOVA was significant $F(15,246) = 3.99, p < .001$. Univariate ANOVA's documented significant differences on all of the variables. On all of the variables, with the exception of the recognition trial the Control and PTSD groups were significantly different from the SZ and SZP groups. On the recognition section the SZP group scored closely enough to the Control and PTSD group that it was not a significant

difference. While the differences did not attain significance throughout all of the free recall trials, the Control group scored higher than the PTSD group. Similarly, as in the verbal memory domain, the SZP group consistently scored higher than the SZ group.

Once again, a series of MANCOVA's were performed to evaluate the effects of age, education, and psychiatric symptoms. Age and education were not significant covariates. The effect for group was still significant $F(15,240) = 3.55, p < .001$. Similar analyses were then accomplished for symptom variables, the SANS, SAPS and the PCL. The results of these analyses indicated that the SANS $F(5,76) = 1.81, p = .12$, SAPS $F(5,76) = .81, p = .55$, and the PCL $F(5,76) = .73, p = .60$ were not significant. See Table 12 for a comparison of the corrected and uncorrected statistics on the Visual Learning/Memory domain. Finally, recognition scores were ranked and entered in the ANOVA because of the violations of normality. The ANOVA remained significant $F(3,82) = 10.57, p < .001$, indicating that the violation of normality did not influence the results from initial parametric analyses. The recognition scores were still significantly different between the groups.

Emotional Learning/Memory

A MANOVA was used again to compare the groups on the final memory domain, Emotional Memory. The overall MANOVA was significant $F(15,258) = 4.08, p < .001$. All of the univariate analyses were also significant. Post-hoc analyses indicated that the Control and PTSD groups were statistically different from the SZ and SZP groups.

Once again, MANCOVA's were used to analyze the effects of age and education on emotional learning. The univariate analysis for age was not significant $F(5,82) = 1.29, p = .28$, and the univariate analysis for education was not significant $F(5,82) = 1.76, p =$

.13. Similar analyses were then accomplished for symptom variables, the SANS, SAPS and the PCL. The results of these analyses indicated that the SANS was not a significant covariate $F(5,80) = 2.16, p = .07$, nor was the SAPS $F(5,80) = 1.38, p = .24$, or the PCL $F(5,80) = .91, p = .48$. See table 13 for a comparison of the corrected and uncorrected means on the Emotional Learning/Memory domain.

Working Memory

With regard to the MANOVA for the Working Memory domain, the overall MANOVA was significant, indicating significant differences between the groups. See Table 5 for a description of group performances for the Working Memory domain measures. Univariate ANCOVA's yielded significant values for all of the working memory measures. Scheffe post-hoc analyses indicated that the Control and PTSD groups scored significantly higher on all of the subtests than the SZ and SZP groups, with the exception of the Spatial Span Backwards subtest in which the PTSD group did not score significantly higher than the SZP group. None of the comparisons were significant between the PTSD and Control group or between the SZ and SZP groups.

Once again, a series of MANCOVA's were performed to evaluate the effects of age, education, and psychiatric symptoms on the Working Memory domain because of the differences between the groups on these variables. The univariate analysis for age was not significant $F(4,82) = 1.45, p = .23$, but the univariate analysis for education was significant $F(4,82) = 2.78, p < .05$, however, the overall effect for group remained significant $F(12,252) = 3.97, p < .001$. In determining how the covariates influenced the Working Memory domain, between subjects effects indicated that education was a significant covariate on Digit Span Backward and on the Spatial Span Backward scores,

suggesting that there is an association between education and more complex working memory tasks, as the backward portions require the ability to hold and manipulate information rather than just recalling strings of stimuli as in the forward task. Once again, the pattern of differences among the groups remained the same and there were only small changes in the descriptive statistics based on the weighted means. See Table 10 for a comparison of the descriptive statistics for weighted and unweighted means.

Similar analyses were then accomplished for symptoms variables, the SANS, SAPS and the PCL. The results of these analyses indicated that the SANS was a significant covariate, $F(4,81) = 3.41, p < .05$. On the other hand, neither the SAPS $F(4,81) = 1.75, p = .15$, or the PCL $F(4,81) = .46, p = .76$ were significant. Since the SANS was the only covariate exerting an effect upon the variables, another MANCOVA was run with only the SANS as the covariate. This MANCOVA was significant $F(4,58) = 3.09, p < .05$. The SANS was significant on the Spatial Span Forward. The overall effect of group was still significant, $F(8,118) = 3.13, p < .01$. See Table 10 for a comparison of the corrected and uncorrected means on the Working Memory domain.

Executive Function

MANOVA was then used to compare the groups on the Executive Function domain. See Table 6 for descriptive statistics on the Executive Function domain. The overall MANOVA was significant, $F(15,258) = 4.28, p < .001$. Post-hoc analyses indicated that, in general, significant differences were present between the Control and PTSD groups and the SZ and SZP groups. There were two occasions when this was not the case. On the number of categories completed on the WCST, the PTSD group did not

significantly differ from the SZP group. Also on the COWAT FAS total the Control group did not significantly differ from the SZ group.

The MANCOVA's using age and education as the covariates were not significant for age $F(5,82) = 1.94, p = .10$, or for education $F(5,82) = 1.51, p = .20$. The effect for group was still significant $F(15,252) = 3.81, p < .001$. The MANCOVA using the symptom measures as covariates indicated that the SANS was a significant covariate $F(5,80) = 2.56, p < .05$, although the SAPS and the PCL were not significant covariates, $F(5,80) = 1.64, p = .16$, and $F(5,80) = .35, p = .88$, respectively. Because the SANS was the only symptom measure to exert a significant effect on the executive function measures, the MANCOVA was run again, using only the SANS as the covariate. The MANCOVA was significant, $F(2,57) = 2.08, p = .16$. The SANS significantly influenced the Trail Making Test Part B and the COWAT Animal scores. The overall effect for group was significant $F(10,116) = 2.29, p < .02$. See Table 14 for the corrected and uncorrected means on the Executive Function domain.

Attention

A MANOVA was used to compare the groups on the final neurocognitive domain, Attention, see Table 7. The overall MANOVA was significant $F(6,174) = 6.59, p < .001$. The univariate statistics were also significant on both of the measures, the Stroop $F(3,91) = 9.64, p < .001$, and Trails A $F(3,91) = 5.20, p < .01$. Post-hoc analyses indicated that the PTSD group was significantly better different than the SZ and SZP groups on the Trails A. The Control group performed significantly better than the SZ group. On the Stroop, the PTSD and Control group performed significantly better than the SZP group. Inspection of the descriptive statistics suggests that the presence of PTSD

may increase attention as measured by the Trail Making Test part A. On the Stroop we see the same pattern where the PTSD and SZP groups score lower than the Control group and SZ group, respectively. Lower scores on the Stroop reflect poorer accuracy, suggesting that PTSD influences accuracy.

The MANCOVA with age and education as the covariates was significant for age $F(2,84) = 3.65, p < .05$, but not for education $F(2,84) = 2.94, p = .06$, although it approached significance. The overall effect for group was still significant $F(6,170) = 4.80, p < .001$. Inspection of the between subjects effects indicated that age and education significantly influenced the Trails A scores. The symptom measures MANCOVA was significant for the SANS $F(2,82) = 5.75, p < .01$. The SAPS and PCL were not significant $F(2,82) = .68, p = .51$, and $F(2,82) = 1.35, p = .27$. Because the SANS was the only symptom measure to exert a significant effect on the attention measures, the MANCOVA was run again, using only the SANS as the covariate. The MANCOVA was significant, $F(2,59) = 4.53, p < .05$ and the SANS significantly influenced Stroop scores. The overall effect for group was still significant $F(4,120) = 2.61, p < .05$. See Table 15 for a comparison of the corrected and uncorrected means on the Attention Domain.

Since the Trail Making Test part A and the Stroop total score violated the assumptions of normality, scores were ranked and the analyses were conducted again, to correct for the violations in the assumptions of normality. The MANOVA was significant $F(6,174) = 7.71, p < .001$. Univariate tests were also significant for both variables. Post-hoc analyses indicated that the Control and PTSD group were significantly different from the SZ and SZP groups on Trails A scores. On the Stroop,

the Controls were significantly different from the SZP group, indicating that the SZP group made the most errors and the Control group made the least errors. Overall results of the non-parametric tests support findings of parametric analyses.

Hypothesis four:

The SZ and SZP groups will have significantly lower scores on the WAIS-III subscales: Information, Vocabulary and Block Design.

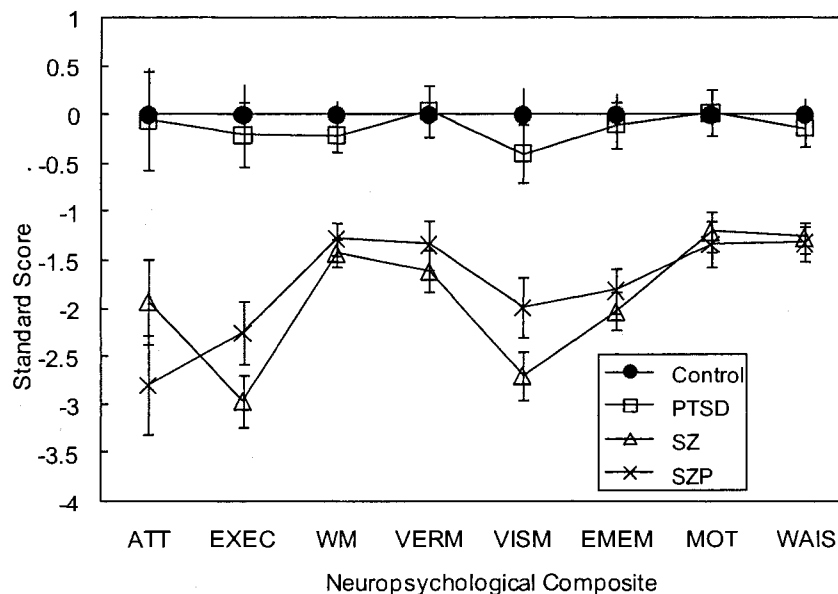
A MANOVA was used to compare the groups on subtests from the WAIS, measures of cognitive function, see Table 8. The overall MANOVA was significant $F(9,261) = 4.74, p < .001$. Scheffe post-hoc analyses yielded significant differences between the Control and PTSD group and the SZ and SZP groups. The Control group was not significantly different than the PTSD group and the SZ and SZP groups were not significantly different from one another. The MANCOVA with age and education as covariates was significant for age $F(3,83) = 3.65, p < .05$. Between subjects effects showed that age was a significant covariate on the Block Design subtest. The impact of group, however, was still significant $F(9,255) = 3.43, p < .001$. Education was not a significant covariate $F(3,83) = 2.08, p = .11$.

Figure 4 summarizes the results for the hypotheses examining the neurocognitive domains. The figure present composite scores for each domain. The scores for each domain were standardized based on the Control group's performance, so that comparisons can be made across the domains for the Control, PTSD, SZ and SZP groups. As can be seen from Figure 4, the SZP and SZ group performed similarly on all of the domains with the exception of the Attention Domain, Executive Function, and Visual Memory Domains. The SZP group exhibited better performance than the SZ group on

the Executive Function and Visual Memory Domains, but performed more poorly on the Attention Domain, showing an interactive effect of PTSD on SZ. In comparing the Control and PTSD groups, the PTSD exhibited slightly poorer performance on the Visual Memory domain, and to a smaller extent on the Executive Function and Working Memory Domains. See Table 16 for comparison for adjusted and unadjusted means.

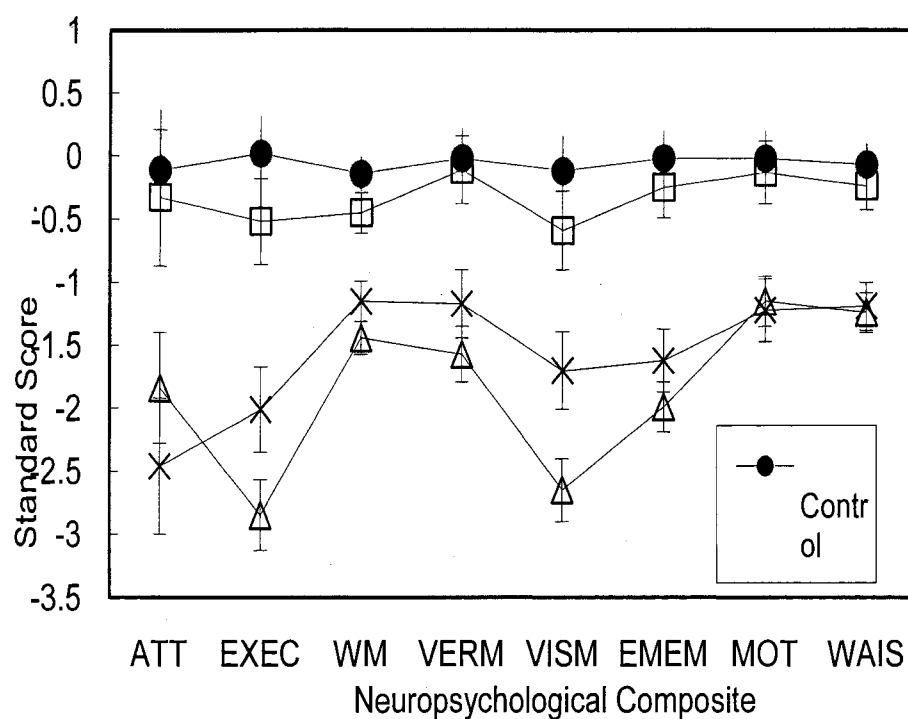
Figure 5 presents the composite scores for the neurocognitive domains as described above and then adjusted for age and education. As can be seen from Figure 5, the pattern of results parallels those described in Figure 4. The corrections for age and education tended to increase the differences in performance between the Controls and PTSD group and the SZ and SZP groups.

Figure 3. Neuropsychological composite scores of each of the groups on all of the neurocognitive domains.



Note. ATT = Attention; EXEC = Executive Function; WM = Working Memory; VERM = Verbal Memory; VISM = Visual Memory; EMEM = Emotional Memory; MOT = Motor Function; WAIS = Intelligence Function.

Figure 4. Neuropsychological composite scores corrected for age and education for each of the groups on all of the neurocognitive domains.



Note. ATT = Attention; EXEC = Executive Function; WM = Working Memory; VERM = Verbal Memory; VISM = Visual Memory; EMEM = Emotional Memory; MOT = Motor Function; WAIS = Intelligence Function.

CHATER 5

DISCUSSION

This study examined the neurocognitive function in individuals with comorbid schizophrenia and PTSD in order to determine if the presence of PTSD caused an increased level of neurocognitive dysfunction, and if present, whether this increased impairment supported either an additive or synergistic model of impairment. The additive model would predict that neurocognitive deficits in the comorbid group would simply reflect the addition of the deficits associated with PTSD to those already present as a result of schizophrenia. On the other hand, the synergistic model would reflect an interaction between the two disorders such that the neurocognitive deficits associated with the comorbid disorder would be much greater than what might be expected from the simple addition of the corresponding impairment associated with each disorder. This study also attempted to further clarify the specific neuropsychological deficits that exist in individuals with PTSD and schizophrenia. Four specific hypotheses were explored to answer these questions. The hypotheses were partially supported by the data and will be discussed individually in terms of the specific findings and potential implications.

Hypothesis One

The first hypothesis examined the psychiatric symptoms associated with each of the three clinical groups. As indicated by prior literature, it was expected that the comorbid group would evidence higher levels of positive symptoms and higher levels of

overall psychiatric distress than the other groups. The MANOVA examining differences among the SZ, SZP and PTSD groups on positive symptoms was significant. As predicted, the PTSD group scored the lowest on all of the global domain scores of the SAPS. On the delusions global rating, the SZP group had significantly more delusions than either the SZ or PTSD groups, findings consistent with Ross, Anderson and Clark (1994) who found increased positive symptoms in individuals with a history of childhood abuse.

The SZP group was also predicted to have fewer negative symptoms than the SZ group. This prediction was only partially supported. On the overall SANS total and the affective flattening subscale the SZP group scored lower than the SZ group. The other subscale scores were not significant. In the only study addressing the influence of comorbid trauma on negative symptoms in schizophrenia did not find any differences in the level of negative symptoms associated with a trauma history (Schellar-Gilkey, Thomas, Woolwine, & Miller, 2002). However, this same study by Schellar-Gilkey and coworkers also did not find significant differences in the level of positive of symptoms, although such differences were present in the current study. In that study, two groups of patients with schizophrenia were compared, one that had comorbid substance abuse, and another that did not. Those with comorbid substance use disorders had more frequently experienced childhood trauma and attained higher scores on measures of PTSD symptoms. However, direct comparisons were not made between patients with schizophrenia who did or did not have PTSD.

It was also predicted that the SZP group would have higher levels of overall psychiatric distress. The BPRS as a measure of overall psychiatric symptoms provided

partial support for this hypothesis, as the scores on the BPRS were significantly different between the groups. The PTSD group had the lowest level of overall symptoms followed by the SZ group. The difference between the SZ and SZP groups were not significant although the means were in the predicted direction. This finding of increased levels of overall psychiatric distress was consistent with the findings of Kim, Kaspar, Noh and Nam (2006) who found increased levels of distress in individuals with a history of physical and sexual abuse.

With regard to depression, the SZ group received the lowest scores on the CDS, indicating the least amount of depressive symptoms, followed by the PTSD group, with the comorbid group attaining the highest level of depressive symptoms. These results were somewhat surprising in that the PTSD group had higher levels of symptoms than the SZ group. This finding does, however, make sense in light of the affective component associated with trauma and PTSD. Furthermore, the increase in depressive symptoms associated with a trauma history may be related to the increased risk of suicidality associated with comorbid schizophrenia and PTSD documented by Read and Ross (2003).

On the PCL which measures symptoms specific to PTSD, the SZ group had the lowest score reflecting lower symptoms, while the SZP group had the highest level of symptoms. The differences between all three groups were significant. Craine, Henson, Colliver and MacLean (1988) also documented symptoms commonly linked to trauma history in individuals with severe mental illness and a sexual abuse history, although they did not compare the individuals in their sample to a PTSD group, thereby making it unclear if the SZP group would have had more symptoms than a PTSD only group.

Additionally, Resnick, Bond and Mueser (2003) obtained similar results and further documented that levels of PTSD symptoms are related to increased severity of trauma, or increased instances of trauma. The majority of the sample in this study was exposed to more than one traumatic event. In fact, 43% of the PTSD sample had been traumatized only once, while 14% of the individuals in the SZP group were exposed to only one traumatic event. Studies have shown that multiple traumatization is associated with more severe symptoms and so it is possible that these groups may have exhibited increased levels of symptoms resulting from multiple traumatizations (Classen, Palesh, & Aggaral, 2005).

In summary, results of symptom ratings suggest that the presence of PTSD in schizophrenia is associated with increased positive symptoms, increased PTSD symptoms, increased depression, and increased levels of more generalized symptoms of psychiatric distress. On the other hand, the presence of PTSD in schizophrenia was associated with slightly decreased levels of negative symptoms.

Hypothesis Two

The second hypothesis evaluated motor performance among the groups. Motor performance was not expected to be impaired in the PTSD group or to impact the performance in the SZP group, because deficits in motor function are not associated with PTSD. As predicted, there were no significant differences between the SZP and SZ groups, although both groups performed more poorly than the Control and PTSD groups who did not differ from each other.

On the Finger Tapping Test there were no differences on the pattern of performance between the Control and PTSD groups. Similarly, there were no differences

between the PTSD group and the Control group on the Purdue Pegboard. The SZP group performed high enough so that the mean was no longer significantly different from the Controls or PTSD group for either the dominant or non-dominant hands. On the trial using both hands, the pattern was the same, but there was greater disparity between the scores of the Control and PTSD groups and the SZ and SZP groups. Overall results of motor function are somewhat conflicting. However, it is not unusual to observe these types of inconsistencies between dominant and non dominant hands on various motor tasks (Jarvis & Barth, 1994), necessitating the use of multiple measures of motor function as was used in the current study. These inconsistencies between dominant and nondominant hand performance do however suggest that there was no strong evidence of lateralized dysfunction in these patients.

As predicted the Control and PTSD group exhibited similar performance across the motor measures. Additionally, the SZ and SZP groups exhibited similar patterns of performance. Interestingly, on the individual hand trials of the Purdue Pegboard the SZP group scored in between the scores from the PTSD group, Control group and the SZ group. This finding may reflect that the motor performance associated with SZP is less severe than that associated with schizophrenia, but as the task demands become more difficult or complex, the compromised resources associated with schizophrenia limit the performance by the SZP group, impairing performance.

Hypothesis Three

This hypothesis was designed to evaluate the pattern of neurocognitive performance associated with the four groups (Controls, PTSD, SZ and SZP).

Neurocognitive performance was assessed using six domains: Attention, Working

Memory, Executive Function, Verbal Learning/Memory, Visual Learning/Memory, and Emotional Learning/Memory. It was predicted that the PTSD group would exhibit some minor impairment in these domains, particularly on the Attention, Working Memory, Executive Function and Verbal Learning/Memory domains based on prior research (Jenkins, Langlais, Delis, & Cohen, 1998; Yehuda, Golier, Halligan, & Harvey, 2004). Furthermore, both of the schizophrenia groups were predicted to perform more poorly than the Control and PTSD groups, with the SZP group exhibiting the worst performance due to the combined effects of schizophrenia and PTSD on neurocognitive function.

Consistent with this hypothesis, the SZ groups had significantly more impairment than the Control and PTSD groups on all of the neurocognitive domains. The PTSD group did not significantly differ from the Control group on any of the neurocognitive domains. These non-significant differences may reflect the inconsistencies in neurocognitive function reflected in the literature on PTSD. For example, although explicit verbal memory is the most researched area of neurocognitive function in PTSD, many studies have not found significant differences between PTSD groups and controls (Neylan et al., 2004; Stein, Hanna, Vaerum, & Koverola, 1999). Other research has suggested that results of the whole group may be confounded because only specific subsets of individuals with PTSD experience cognitive deficits (Sutker, Vasterling, Brailey, & Allain, 1995). In their sample it was only POW's with PTSD and who had high levels of arousal dysregulation that experienced cognitive deficits. Other research has suggested that cognitive deficits associated with PTSD would be related to current PTSD versus lifetime PTSD diagnosis, because the cognitive deficits may become less severe or reverse completely with the passing of time or through the use of medication

(Seedat et al., 2002). Additionally, levels of cognitive impairment may be related to the time in development when the traumatic event occurred (Bremner & Vermetten, 2001), so that individuals who experience trauma at younger ages are more likely to have neurostructural and neurophysiological abnormalities than those affected at older ages. As discussed in the literature review, different types of traumatic events are associated with increased levels of PTSD and potentially different levels of cognitive dysfunction. Since the PTSD group in this study was heterogeneous there may have been fewer neurocognitive impairments than a PTSD group composed of only rape survivors for example.

The second domain that the PTSD group would be expected to exhibit impairment is the Attention Domain (Gilbertson, Gurvits, Lasko, Orr & Pitman, 2001). Once again there was no significant difference between the Control and the PTSD group on the Attention Domain, although the SZP group did perform worse than the SZ group for this domain. In fact, this was the only instance in which the SZP group performed noticeably worse than the SZ group (although the difference was not significant). A possible explanation may be that SZP increases attention through hyperarousal. Hyperarousal has been associated with decreased accuracy or more false alarms based on the increased vigilance (Wilding, Pankhania, & Williams, 2007). This hypothesis could also be examined using reaction times. Wilding, Pankhania, and Williams, however, did not find any differences in reaction times associated with increased arousal. Additionally, all groups exhibited relatively high levels of accuracy decreasing the ability to detect true differences between the groups. This does, however, suggest that the differences between the SZP and SZ group may be greater with a measure with greater variability in

scores. Additionally, the Attention Domain did not include a measure of sustained attention, which may result in a different pattern of performance. Koso and Hansen (2006) examined sustained attention and found impaired attention.

On the two other domains most related to frontal lobe function, Executive Function and Working Memory, results between the PTSD and Control groups were similar. Additionally, there were slight differences between the PTSD group and Controls on the Visual Learning/Memory domain. There are only a few studies, which have addressed the neurocognitive domain of Visual learning/memory. Bremner, Vermetten, Afzal and Vythillingham (2004) and Jelinek et al. (2006) both documented Visual Learning/Memory deficits in women with a history of childhood sexual abuse, whereas Yasik, Saigh, Oberfield and Halamandaris (2007) did not find any differences in adolescents with PTSD. In summary, the PTSD group did not exhibit impaired performance on any of the neurocognitive domains. There did appear to be a potential effect of trauma on Visual Learning/Memory, Working Memory, and Attention, which are areas to investigate further.

As predicted the SZ and SZP group exhibited significantly lower performance than the Controls and PTSD group. There were a number of instances where the SZ or SZP group scored closely enough to either the PTSD or Control group so that the difference was no longer significant. The recognition trial on the explicit verbal memory test was not significantly different between any of the groups. The SZP group was not significantly different from the control or PTSD groups on the visual memory recognition trial. Other times when the SZP group was not significantly different from the PTSD group, were on the Backward Spatial Span test in the Working Memory domain and on

the percent perseverative errors on the WCST. The Control group was not significantly different from the SZ group on the FAS total or on the Trail Making Test part A. Some possible explanations will be made regarding these differences in the following sections discussing the performance separately for each domain.

In addition to the hypothesis that the SZ and SZP groups would demonstrate differences on all of the domains, it was hypothesized that the SZP group would exhibit the highest level of impairment based on both the additive and the synergistic models. Consistent with the hypothesis, the SZ and SZP groups differed from the PTSD and Control groups across all domains, with a few minor exceptions for particular measures as discussed above. However, contrary to the hypothesis, the SZP and SZ groups did not differ significantly from one another in neurocognitive performance. The only consistent pattern was that the SZP group scored slightly higher than the SZ group on all of the neurocognitive domains, with the exception of the Attention domain.

The SZP group performed one standard deviation higher than the SZ group on the Visual/Learning and Memory domain. This is in sharp contrast to the performance of the PTSD group relative to their comparative group, who performed more poorly than the Controls. Similarly, the SZP group scored slightly higher than the SZ group on the Executive Function domain. Once again, this is an area in which the PTSD performance was slightly lower than the Controls. Finally, the last notable comparison between the SZP and SZ group was on the Attention domain, representing an interaction effect between the groups. On the Attention domain, the SZP group performed more poorly than the SZ group. It is unclear as to what these slight differences in performance between the SZ and SZP group mean. It would seem that the issue warrants some further

investigation. It may be that individuals with schizophrenia who have particularly poor attentional abilities are more prone to develop PTSD when exposed to trauma, or alternatively that trauma and its associated neuropathophysiology expresses itself uniquely as an impairment in attention. Performance on the Attention domain was in the predicted direction with the SZP group performing more poorly than the SZ group. Somewhat surprisingly the SZP group performed relatively better than the SZ group on Executive Function and Visual Learning/Memory and not consistent with the pattern of performance on these domains in the PTSD group. The comparisons would seem to suggest that the PTSD influences performance differently in individuals with and without comorbid schizophrenia. At least, in this sample of individuals with comorbid schizophrenia and PTSD, the presence of PTSD did not negatively influence the neurocognitive performance associated with SZ in most domains. When solely comparing the mean scores, PTSD even appeared to have a mitigating effect on neurocognitive tests, with the exception of the Attention domain. Because the presence of comorbid PTSD did not produce a consistent pattern of more severe neurocognitive impairment, neither the additive or synergistic model was supported.

The same comparisons for performance of the groups across neurocognitive domains were then conducted using two different covariate analyses. The effects of age and education were examined in the first model and the effects of symptoms measures, in particular the scores on the SANS, SAPS and PCL, was examined in the second model. The following section, will describe the significant results of these MANCOVA's. On the Verbal Memory Domain, the SANS was a significant predictor. Univariate analyses indicated that the SANS significantly influenced the trials 1-5 scores, the short delay trial

and the long delay trial. On the MANCOVA, for the Working Memory domain, covariate analyses indicated that education was a significant covariate and that it exerted effects on the backward sections of the both the Digit Span and the Spatial Span. Covariate analyses utilizing the symptom measures were significant for negative symptoms, in particular on the Spatial Span Forward. On the Executive Function domain, the only significant predictor was the SANS, although the effect of group was still significant. Univariate analyses indicated that the SANS significantly influenced Trails B scores and the COWAT Animals named. On the Attention Domain using age and education as covariates, the effect for group remained significant, but age was a significant predictor and education was marginally significant ($p = .06$). Both variables contributed to performance on the Trail Making Test. Negative symptoms were significant, with univariate analyses indicating that negative symptoms significantly influence Stroop scores. Overall results of MANCOVA's demonstrated that negative symptoms exerted the greatest influence on neurocognitive performance.

Hypothesis Four

As predicted in this hypothesis, the presence of PTSD did not influence performance on the WAIS subscales. The PTSD and Control group performed similarly and the SZ and SZP groups performed similarly. In evaluating the impact of age, education, and symptom ratings, education was the only variable to significantly impact one of the subtests. Education had a significant influence on the Block Design subtest, which is consistent with a large number of studies indicating that education is significantly predictive of performance on tests of intelligence.

The data for all of the domains including motor function and the WAIS subtests were converted to z-scores to make overall comparisons between the groups. Figure 4 depicts the performance of each group for all eight domains. As discussed in each of the separate domains, the PTSD and Control group scored similarly. In comparing the two groups across domains, the largest differences were on the Visual Learning/Memory domain, followed by the Executive Function and Working Memory domains, with the PTSD group scoring lower than the Control group. These results should be interpreted cautiously because the majority of the comparisons made in this study were not statistically significant.

Strengths of the Study

This investigation makes an important contribution to the literature in that it is among the first to examine neurocognitive performance in individuals with comorbid schizophrenia and PTSD. Furthermore, this study utilized a comprehensive battery of neuropsychological tests to assess all areas of function which have been implicated in the pathophysiology of either schizophrenia or PTSD. Also, comprehensive assessment of symptoms were conducted and rigorous diagnostic evaluations were implemented with all participants. Another strength of this study is that its four group design included appropriate control groups for the samples affected by PTSD (both a normal control group and a schizophrenia control group), which allowed for specific comparisons of neurocognitive performance associated with the comorbid group and with each disorder singly.

When considering all of the neurocognitive abilities assessed, comorbid PTSD exerted its greatest influence on the Attention, Executive Function and Visual

Learning/Memory domains. While the differences between the SZ and SZP groups were not significant, a number of interesting patterns emerged. First, the comorbid group had poorer performance on the Attention domain, but scored higher on the Executive Function and Visual Learning/Memory domain. While not significant, the difference between the SZ and SZP groups averages approximately one standard deviation, so it is likely that these differences would become significant with more participants. For the PTSD only group, the potential impairment of Visual Learning/Memory was also a relatively new finding that has not been explored extensively in the literature.

Another important contribution of the study is the examination of psychiatric symptoms among the three clinical groups. The presence of comorbid PTSD significantly impacted psychiatric symptoms. The SZP group had higher levels of positive symptoms (hallucinations, delusions), a finding consistent with the literature (Ross, Anderson & Clark, 1994; Beck & van der Kolk, 1987; Craine et al., 1988). This study may be the first to also determine that the presence of comorbid PTSD is associated with fewer negative symptoms. The SZP group also had the highest scores on the BPRS, another more general measure of psychiatric distress. Additionally, as might be expected the SZP received higher scores on the measure of PTSD symptoms. The SZP group also received higher scores on the PTSD measure than the PTSD only group. Finally, the pattern of performance was the same on a measure of depressive symptoms with the SZP group scoring the highest, followed by the PTSD group. Increased levels of depression have also been documented in individuals with comorbid schizophrenia and may be associated with increased suicidality. These findings certainly have implication for treatment, and future studies may further elaborate on the current findings by examining

the impact of comorbid PTSD in response to various behavioral and pharmacological interventions.

Limitations

Several limitations were identified in the current investigation. The number of individuals in each of the groups was small, ranging from 21 to 26, contributing to potentially decreased statistical power to detect differences among the groups. Other studies to evaluate comorbid schizophrenia and PTSD have used comparable sample sizes, although some have used larger samples (Scheller-Gilkey et al., 2004). However, it is important to note that many of these studies have not examined patients who carried diagnoses of PTSD, but rather made dichotomies between those who had experienced a traumatic event at some point in their lives, and those who had not. It is apparent that meaningful differences do exist between those who develop PTSD after experiencing trauma, and those who do not. So, while limited by a small number of cases in each group, the current study provides valuable information on the effects of PTSD in schizophrenia. Also, despite the limited sample size, significant differences were found in the current study among the groups on several neurocognitive measures. Future studies, however, should attempt to include larger sample sizes to optimize the findings and inferences.

The selection process in itself may have posed a threat to internal validity, particularly with regard to the PTSD sample. The individuals in the two schizophrenia groups and the controls were recruited from Mojave Mental Health and the community, whereas the PTSD group was composed primarily of undergraduate psychology students from the University of Nevada, Las Vegas. In general, the PTSD participants were high

functioning, with only mild to moderate PTSD. There is likely to have been a selection bias in the PTSD individuals who chose to participate. Studies investigating PTSD have documented that individuals who chose to participate in research are usually farther along in the recovery process and are potentially using the study as a way to help others (Newman & Kaloupek, 2004). In light of the relatively high functioning sample of individuals with PTSD, significant differences between the PTSD and Control group may not have been detected. Similarly, the heterogeneity of trauma type may have contributed to fewer neurocognitive deficits, in that specific types of trauma (e.g., rape) are more likely to cause neurocognitive deficits. The differences between the PTSD and Control group are expected to be even greater when individuals with more severe traumatic event types are evaluated.

Similarly, the magnitude of differences may have been minimized because the PTSD and SZP groups were composed of individuals who had either a lifetime diagnosis of PTSD or a current diagnosis of PTSD. It is anticipated that those with a current diagnosis would exhibit more severe symptoms, both psychiatric and neurocognitive. In order to at least preliminarily investigate this potential explanation, the PTSD and SZP groups were broken down into a current PTSD group, a lifetime PTSD group, a current SZP group and a lifetime SZP group. The PTSD and SZP groups were compared separately using MANOVA's on the composite scores for the domains. In the PTSD only group there were no significant differences across the domains for a lifetime diagnosis versus a current diagnosis. It did appear that the results might have been significant if there was a larger sample. The comparison on the domains for the current and lifetime diagnosis in the PTSD group suggested that a current diagnosis of PTSD

impacted performance on all of the domains in a negative manner. The largest differences in performance were on the Verbal Learning/Memory domain, the Visual Learning/Memory domain, Executive Function, and Attention. When the same analysis was run in the SZP group, the current diagnosis of PTSD was associated with increased performance on the Executive Function and Motor domain. Performance was decreased by the presence of current PTSD on the Attention domain. These differences were not significant. Once again, the sample sizes were small with an $n = 13$ and an $n = 8$.

Another consideration in regards to the sample is that both schizophrenia groups had high rates of traumatic events. Individuals could be included in the SZ group if they had a prior history of trauma, but did not ever have significant distress consistent with a PTSD diagnosis. A history of trauma was not part of the exclusionary criteria for the SZ group based on the high prevalence rates of traumatic events in those individuals with schizophrenia.

Significance of the Study/ Conclusions

As mentioned before, this is among the first studies examining neurocognitive impairment associated with comorbid schizophrenia and PTSD. Clarification of neurocognitive functioning in individuals with comorbid schizophrenia and PTSD is increasingly important for both theoretical and practical reasons. From a theoretical standpoint, characterizing the unique strengths and deficits of these patients provides insight into underlying pathophysiology and gives direction to research investigating discrete neurocognitive deficits as potential endophenotypes for psychiatric disorders. Since both PTSD and schizophrenia are complex polygenic disorders that exhibit

imperfect penetrance, neurocognitive abilities have been suggested as endophenotypes because they are highly heritable.

From a practical standpoint, there is increasing evidence linking neurocognitive abilities to functional outcomes in schizophrenia (Green, Kern, and Heaton, 2004). Identifying unique neurocognitive deficits will allow for the development of treatments whose aim is to remediate those deficits and thus improve functioning. Furthermore, there are few studies which have examined the impact of PTSD in schizophrenia on psychiatric symptoms. Psychiatric symptoms may lead to increased hospitalization, substance abuse, and suicidality, and so the characterization provided here lays the groundwork for studies with larger samples whose goals are to link specific treatment with specific symptoms. Future studies should examine these issues further, to more clearly determine the role of specific cognitive impairments on functional outcomes and response to treatment.

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TABLES

Table 1. Demographic characteristics for the Normal Control (C), Post-Traumatic Stress Disorder (PTSD), Schizophrenia (SZ), and Schizophrenia with PTSD (SZP) groups.

Variable	Group				<i>F</i> df=3,8 8	<i>P</i>	Scheffe <i>P</i> < .05
	C	PTSD	SZ	SZP			
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)			
Age	36.3 (13.2)	26.6 (13.2)	39.5 (10.4)	40.7 (8.6)	6.60	.00	PTSD < SZ, SZP
Education	13.2 (1.3)	13.1 (1.0)	12.8 (1.5)	12.1 (1.0)	3.15	.03	None
	N (%)	N (%)			$\chi^2(21)$ 28.55	<i>P</i> NS	
Ethnicity							
Asian	1 (4)	1 (5)	1 (4)	1 (5)			
American African	1 (4)	3 (14)	12 (46)	3 (14)			
American Biracial	3 (12.5)	3 (14)	1 (4)	2 (9.5)			
European	16 (66)	10 (48)	11 (42)	12 (57)			
American Hispanic	2 (8)	1 (5)	1 (4)	1 (5)			
American Native	0 (0)	2 (10)	0 (0)	1 (5)			
American Pacific Islander	0 (0)	1 (5)	0 (0)	0 (0)			
Other	1 (4)	0 (0)	0 (0)	2 (10)			
Sex					10.24	.02	
Male	7	7	18	7			
Female	17	12	8	14			

Note: C (n = 24), PTSD (n = 21), SZ (n = 26), SZP (n = 21).

Table 2. Symptom ratings for the PTSD, SZ, and SZP groups.

Variable	PTSD (P)		SZ		SZP		<i>F</i> (2, 67)	<i>p</i>	Scheffe <i>Post-hoc</i>
	Mean	SD	Mean	SD	Mean	SD			
SANS									
Total Score	3.10	4.60	12.27	6.10	9.50	4.69			
Affective flattening	0.52	0.81	3.00	1.36	1.85	1.31	24.84	.001	P<SZP<SZ
Alogia	0.14	0.48	1.96	1.51	1.45	1.43	12.64	.001	P<SZP,SZ
Avolition-apathy	0.48	0.87	2.15	1.71	1.85	1.35	9.22	.001	P<SZP,SZ
Anhedonia-asociality	0.52	0.75	2.50	1.48	1.80	1.67	12.33	.001	P<SZP,SZ
Attention	0.38	0.50	2.70	1.33	2.55	1.05	32.87	.001	P<SZP,SZ
SAPS									
Total Score	1.48	2.50	7.81	3.14	8.65	2.30			
Hallucinations	0.24	0.63	1.96	1.69	2.95	1.50	20.48	.001	P<SZ,SZP
Delusions	0.14	0.16	2.50	.91	3.70	.80	123.18	.001	P<SZ<SZP
Bizarre behavior	0.48	0.98	1.73	1.12	1.05	1.36	6.94	.01	P< SZ
Thought disorder	0.24	0.54	1.62	1.42	.95	1.15	8.73	.001	P< SZ
CDS	4.10	4.05	1.31	1.67	7.71	7.08	16.76	.001	SZ,P<SZP
BPRS Total	29.00	10.17	40.12	6.54	45.43	16.00	11.69	.001	P<SZ,SZP
PCL	34.10	17.08	6.69	13.05	51.86	20.56	42.85	.001	SZ<P<SZP

Note: BPRS = Brief Psychiatric Rating Scale, SANS = Schedule for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms, PCL = Post Traumatic Stress Disorder Checklist, CDS = Calgary Depression Scale.

Table 3. Motor domain performance for Controls (C), PTSD (P), Schizophrenia Controls (SZ), and Comorbid Schizophrenia/PTSD (SZP) groups.

Neuropsychological Tests	Groups						Univariate Tests	Post Hoc Tests: Scheffe
	C		PTSD		SZ			
	Mean	SD	Mean	SD	Mean	SD		
Finger Tapping Dom.	49.46	6.13	48.20	14.82	36.81	14.38	10.03**	C,P>SZ,SZP
Finger Tapping Ndom.	44.71	6.79	46.19	13.48	35.04	11.63	8.53**	P,C>SZ,SZP
Peg Board Dom.	12.96	5.45	13.14	4.00	8.38	2.06	7.89**	C,P>SZ
Peg Board Ndom.	12.38	5.00	12.29	3.50	8.23	3.02	7.40**	P,C>SZ
Peg Board Both	19.46	8.86	20.33	5.89	11.65	5.24	9.92**	P,C>SZP,SZ

Note. ** $p < .001$.

Table 4. Memory domain performance for Controls (C), PTSD (P), Schizophrenia Controls (SZ), and Comorbid Schizophrenia/PTSD (SZP) groups.

Neuropsychological Tests	Groups						Univariate Tests		Post Hoc Tests: Scheffe
	C		PTSD		SZ		SZP		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
<u>Verbal Learning/Memory</u>									
CVLT: Trials 1-5	55.25	9.06	54.24	9.58	29.77	10.88	33.19	15.36	C,P>SZP,SZ
Distractor List	7.25	1.92	7.67	2.03	3.92	1.65	4.10	2.45	P,C>SZP,SZ
Short Delay Free Recall	11.21	2.95	11.62	2.91	5.50	3.53	6.71	4.17	C,P>SZP,SZ
Long Delay Free Recall	11.67	2.76	11.86	2.37	5.12	3.52	6.24	4.38	P,C>SZP,SZ
Recognition	15.29	1.85	14.81	1.86	16.73	6.64	15.76	7.91	SZ,SZP,C,P
<u>Visual Learning/Memory</u>									
Biber: Trials 1-5	140.43	40.08	137.05	48.80	60.27	40.63	71.90	32.14	C,P>SZP,SZ
Distractor List	13.04	7.18	12.16	5.64	4.08	4.39	4.60	2.35	C,P>SZP,SZ
Short Delay Free Recall	34.26	8.32	31.00	11.16	14.27	11.34	16.65	9.85	C,P>SZP,SZ
Long Delay Free Recall	35.39	7.17	32.95	11.00	14.77	10.42	17.80	9.64	C,P>SZP,SZ
Recognition	14.57	.73	13.79	3.49	10.92	4.05	12.55	2.50	C,P>SZ
<u>Emotional Learning/Mem</u>									
EVLT: Trials 1-5	48.67	8.01	45.38	14.60	26.46	10.26	28.67	12.98	C,P>SZP,SZ
Distractor List	5.79	1.64	5.48	1.33	2.92	1.62	3.19	1.40	C,P>SZP,SZ
Short Delay Free Recall	9.46	2.73	9.62	3.07	4.58	2.83	4.81	3.49	P,C>SZP,SZ
Long Delay Free Recall	9.29	2.68	9.38	3.49	3.73	3.19	4.00	3.10	P,C>SZP,SZ
Recognition	14.50	1.98	14.29	2.12	10.96	3.26	10.71	4.46	C,P>SZ,SZP

Note. ** $p < .001$, * $p < .01$

Table 5. Working Memory domain performance for Controls (C), PTSD (P), Schizophrenia Controls (SZ), and Comorbid Schizophrenia/PTSD (SZP) groups.

Neuropsychological Tests	Groups								Univariate Tests	F	Post Hoc Tests: Scheffe
	C		PTSD		SZ		SZP				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Digit Span Forward	10.67	1.81	10.52	2.52	7.85	2.19	7.90	2.17	12.09**	C,P>SZP,SZ	
Digit Span Backward	7.04	1.65	6.52	1.60	4.42	1.84	4.10	1.61	17.65**	C,P>SZ,SZP	
Spatial Span Forward	8.75	2.03	8.19	1.75	6.27	2.49	5.67	1.71	11.92**	C,P>SZP,SZ	
Spatial Span Backward	7.54	2.28	7.14	2.54	4.46	2.25	5.29	1.74	10.54**	C>SZ,SZP; P>SZ	

Note. ** $p < .001$, * $p < .01$

Table 6. Executive Function domain performance for Controls (C), PTSD (P), Schizophrenia Controls (SZ), and Comorbid Schizophrenia/PTSD (SZP) groups.

Neuropsychological Tests	Groups								Univariate Tests	F	Post Hoc Tests: Scheffe
	C		PTSD		SZ		SZP				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
WCST % perseverative	10.92	5.63	17.24	15.01	33.62	22.09	27.05	24.29	7.47**	C<SZP,SZ;P<SZ	
WCST cat. complete	5.29	1.57	4.62	1.80	1.88	2.03	3.20	2.44	14.19**	SZP,SZ<C;SZ<P	
Letter Fluency (FAS)	37.75	9.53	39.10	10.15	28.92	12.77	26.60	9.53	6.12**	C>SZP;P>SZ,SZP	
Category Fluency	19.88	4.10	20.43	3.43	13.62	5.11	13.80	4.00	15.14**	P,C>SZP, SZ	
Trails B	65.71	19.11	62.52	20.24	183.88	85.93	179.15	97.18	23.31**	P,C>SZP,SZ	

Note. ** $p < .001$, * $p < .01$

Table 7. Attention/Psychomotor domain performance for Controls (C), PTSD (P), Schizophrenia Controls (SZ), and Comorbid Schizophrenia/PTSD (SZP) groups.

Neuropsychological Tests	Groups								Univariate Tests	Post Hoc Tests: Scheffe
	C		PTSD		SZ		SZP			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Stroop	79.29	1.43	78.57	3.22	76.65	4.40	73.15	10.06	5.20*	C,P>SZP
Trails Making Test Part A	33.08	11.41	28.57	7.18	56.12	30.28	46.85	19.40	9.64**	P<SZP,SZ;C<SZ

Note. ** $p < .001$, * $p < .01$

Note. ** $p < .001$, * $p < .01$

Table 8. Wechsler subtest performance for Controls (C), PTSD (P), Schizophrenia Controls (SZ), and Comorbid Schizophrenia/PTSD (SZP) groups.

Wechsler Subtests	Groups								Univariate	Post Hoc
	C		PTSD		SZ		SZP			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Tests	
									Tests: Scheffe	
Vocabulary	42.35	12.02	36.90	8.63	26.38	12.72	25.62	12.16	11.43**	C,P>SZ,SZP
Information	16.00	4.84	15.76	4.17	11.08	4.67	10.57	4.58	9.19**	C,P>SZ,SZP
Block Design	37.43	9.52	38.24	14.51	23.50	9.19	23.33	9.42	13.56**	P,C>SZ,SZP

Note. ** $p < .001$, * $p < .01$

Table 9. Comparison of the adjusted and unadjusted means for the Motor Domain.

				Corrected	
				for Age and	
Test	Group	Uncorrected		Education	
Finger Tapping					
Dominant Hand	NC	49.46	6.13	49.65	2.61
	PTSD	48.19	14.82	47.10	2.91
	SZ	36.81	13.38	37.32	2.50
	SZP	32.24	14.85	32.48	2.90
Finger Tapping Non-					
Dominant Hand	NC	44.71	6.78	44.56	2.47
	PTSD	46.19	13.48	44.97	2.76
	SZ	35.04	11.63	35.49	2.37
	SZP	30.86	15.06	31.69	2.75
Pegboard Dominant	NC	12.96	5.45	12.85	.84
	PTSD	13.14	3.97	12.63	.94
	SZ	8.38	2.86	8.56	.80
	SZP	9.86	3.62	10.28	.93
Pegboard Non-Dominant	NC	12.38	4.99	12.22	.78
	PTSD	12.29	5.89	11.84	.87
	SZ	8.23	3.02	8.37	.75
	SZP	9.14	3.44	9.60	.87
Pegboard Both	NC	19.46	8.86	19.33	1.43
	PTSD	20.33	5.89	19.58	1.43
	SZ	11.65	5.24	11.92	1.37
	SZP	12.43	7.30	13.00	1.59

Table 10. Comparison of adjusted and unadjusted means on the Working Memory Domain.

Test	Group	Uncorrected		Corrected for Age and Education		Corrected For SANS Symptom Rating	
		Mean					
Digit Span Forward	NC	10.67	1.81	10.57	.45		
	PTSD	10.52	2.52	10.42	.50	10.50	.61
	SZ	7.85	2.19	7.86	.43	7.83	.50
	SZP	7.85	2.21	8.12	.50	7.85	.52
Digit Span Backward	NC	7.04	1.65	6.89	.33		
	PTSD	6.52	1.60	6.36	.37	6.12	.44
	SZ	4.42	1.84	4.44	.32	4.55	.36
	SZP	4.10	1.65	4.42	.37	4.13	.38
Spatial Span Forward	NC	8.75	2.03	8.68	.42		
	PTSD	8.19	1.75	7.92	.47	7.32	.51
	SZ	6.27	2.49	6.36	.40	6.80	.42
	SZP	5.65	1.76	5.92	.47	5.75	.44
Spatial Span Backward	NC	7.54	2.29	7.39	.44		
	PTSD	7.14	2.54	6.68	.49	6.77	.59
	SZ	4.46	2.25	4.60	.42	4.67	.47
	SZP	5.25	1.78	5.75	.49	5.29	.50

Table 11. Comparison of adjusted and unadjusted means for the Verbal Learning and Memory Domain.

Test	Group	Corrected					
		Uncorrected		for Age and		Corrected	
		Mean		Education		For SANS	
CVLT Trial 1-5	NC	55.25	9.06	54.81	2.35		
	PTSD	54.24	9.58	53.60	2.63	49.63	3.08
	SZ	29.77	10.88	29.89	2.26	32.25	2.49
	SZP	33.19	15.36	34.18	2.62	33.08	2.62
CVLT Distractor List	NC	7.25	1.92	7.15	.41		
	PTSD	7.67	2.03	7.35	.45	7.56	.54
	SZ	3.92	1.65	4.02	.39	4.03	.44
	SZP	4.10	2.45	4.40	.45	3.97	.46
CVLT Short Delay	NC	11.21	2.95	11.11	.71		
	PTSD	11.62	2.91	11.39	.79	10.26	.91
	SZ	5.50	3.52	5.56	.68	6.24	.73
	SZP	6.71	4.17	6.98	.79	6.69	.77
CVLT Long Delay	NC	11.67	2.76	11.54	.69		
	PTSD	11.86	2.37	11.78	.77	10.50	.88
	SZ	5.12	3.53	5.11	.66	5.87	.71
	SZP	6.24	4.38	6.47	.77	6.10	.75
CVLT Recognition	NC	15.29	1.85	15.10	1.10		
	PTSD	14.81	1.86	14.24	1.22	15.01	1.65
	SZ	16.73	6.64	16.90	1.05	16.49	1.33
	SZP	15.76	7.91	16.35	1.22	15.60	1.41

Table 12. Comparison of adjusted and unadjusted means for Visual Learning and Memory Domain.

Test	Group	Corrected			
		Uncorrected		for Age and	
		Mean		Education	
Biber Trial 1-5	NC	140.43	40.08	138.24	8.56
	PTSD	137.05	48.80	132.02	9.80
	SZ	60.27	40.63	61.92	8.02
	SZP	70.21	32.09	77.06	9.54
Biber Distractor List	NC	13.04	7.18	12.88	1.10
	PTSD	12.16	5.64	11.42	1.26
	SZ	4.08	4.39	4.36	1.03
	SZP	4.53	2.39	5.13	1.22
Biber Short Delay	NC	34.26	8.32	33.40	2.11
	PTSD	31.00	11.16	29.21	2.41
	SZ	14.27	11.34	14.84	1.98
	SZP	16.11	9.80	18.61	2.35
Biber Long Delay	NC	35.39	7.17	34.66	2.00
	PTSD	32.95	11.00	31.65	2.29
	SZ	14.77	10.42	15.16	1.88
	SZP	17.47	9.79	19.37	2.23
Biber Recognition	NC	14.57	.73	14.30	.62
	PTSD	13.79	3.49	13.59	.71
	SZ	10.92	4.05	10.94	.58
	SZP	10.92	4.05	13.03	.69

Table 13. Comparison of adjusted and unadjusted means for Emotional Learning and Memory.

Test	Group	Uncorrected		Corrected for Age and Education	
		Mean			
EVLTL Trial 1-5	NC	48.67	8.01	48.35	2.35
	PTSD	45.38	14.60	43.55	2.62
	SZ	24.62	10.26	27.10	2.25
	SZP	28.67	12.98	30.07	2.61
EVLTL Distractor List	NC	5.79	1.64	5.70	.31
	PTSD	5.48	1.33	5.26	.34
	SZ	2.92	1.63	2.98	.29
	SZP	3.19	1.40	3.44	.34
EVLTL Short Delay	NC	9.46	2.73	9.28	.62
	PTSD	9.62	3.07	9.32	.69
	SZ	4.58	2.83	4.64	.59
	SZP	4.81	3.49	5.24	.69
EVLTL Long Delay	NC	9.29	2.68	9.09	.63
	PTSD	9.38	3.49	9.04	.70
	SZ	3.73	3.12	3.80	.60
	SZP	4.00	3.10	4.49	.70
EVLTL Recognition	NC	14.50	1.98	14.31	.63
	PTSD	14.29	2.12	14.10	.71
	SZ	10.97	3.26	10.98	.61
	SZP	10.71	4.46	11.10	.70

Table 14. Comparison of adjusted and unadjusted means for Executive Function Domain.

Test	Group	Uncorrected		Corrected for Age and Education		Corrected For Psychiatric Symptoms (SANS)	
		Mean					
WCST % perseverative							
errors	NC	10.92	5.63	11.14	3.63		
	PTSD	17.24	15.01	20.51	4.05	19.27	5.61
	SZ	33.62	22.09	32.36	3.49	32.87	4.53
	SZP	27.05	24.29	24.46	4.04	26.91	4.78
WCST categories							
completed	NC	5.29	1.57	5.28	.40		
	PTSD	4.62	1.80	4.36	.45	4.46	.56
	SZ	1.88	2.03	1.99	.39	1.93	.45
	SZP	3.20	2.4	3.48	.45	3.21	.48
Trails B	NC	65.71	19.11	65.42	13.65		
	PTSD	62.52	20.24	69.37	15.24	83.55	19.82
	SZ	183.88	85.93	181.01	13.10	170.56	16.00
	SZP	179.15	97.18	171.96	15.19	176.56	16.87
COWAT FAS	NC	37.75	9.53	36.95	2.24		
	PTSD	39.10	10.15	38.00	2.50	36.34	2.91
	SZ	28.92	12.77	29.11	2.15	30.32	2.35
	SZP	26.60	9.53	29.83	2.49	26.87	2.48
COWAT Animals	NC	19.88	4.10	19.66	.90		
	PTSD	20.43	3.43	19.76	1.00	18.78	1.08
	SZ	13.62	5.11	13.82	.86	14.59	.88
	SZP	13.80	4.00	15.04	1.00	13.99	.92

Table 15. Comparison of adjusted and unadjusted means for Attention Domain.

Test	Group	Uncorrected		Corrected for Age and Education		Corrected For Psychiatric Symptoms	
		Mean					
Stroop	NC	79.29	1.43	79.17	1.15		
	PTSD	78.57	3.22	78.35	1.29	77.93	1.71
	SZ	76.65	4.40	76.71	1.10	77.10	1.38
	SZP	73.15	10.06	73.46	1.32	72.88	1.49
Trails A	NC	33.08	11.41	34.60	3.85		
	PTSD	28.57	7.18	33.30	4.31	35.87	5.52
	SZ	56.12	30.28	54.73	3.69	51.07	4.46
	SZP	46.85	19.40	41.86	4.40	47.29	4.83

Table 16. Comparison of adjusted and unadjusted means for the WAIS subscales.

Test	Group	Corrected			
		Uncorrected		for Age and	
		Mean		Education	
Vocabulary	NC	42.35	12.02	41.52	2.40
	PTSD	36.90	8.63	36.71	2.71
	SZ	26.38	12.72	26.23	2.25
	SZP	25.62	12.16	26.92	2.62
Information	NC	16.00	4.84	15.65	.95
	PTSD	15.50	4.17	15.51	1.04
	SZ	11.08	4.67	11.09	.89
	SZP	10.57	4.58	11.20	1.04
Block Design	NC	37.43	9.52	36.88	2.20
	PTSD	37.75	14.51	36.07	2.39
	SZ	23.50	9.19	24.32	2.06
	SZP	23.33	9.42	25.10	2.40

APPENDIX I

MEASURES

Demographic Questionnaire

Please answer the following questions completely and honestly. All of your responses will remain confidential.

1. Birth Date / /
 Month Day Year
2. Gender **Male** **Female**
3. Ethnicity/Race: Asian American American Indian/Alaska Native
 African American Hawaiian/Pacific Islander
 Hispanic/Latino Biracial
 Other
4. Highest Level of Education Completed (Years) (Months)
5. Marital Status: Married Widowed Divorced
 Remarried Separated Never married
6. Usual or last Occupation
7. Usual living arrangements (past 3 yr.):
 With partner and children With partner alone
 With children alone With parents
 With family With friends
 Alone Controlled environment
 No stable arrangements Other
8. How many children do you have?
9. Have you ever been homeless? **Yes** **No**
10. Do you have a twin? **Yes** **No**
11. Are you left handed, right handed, or ambidextrous? **Left** **Right** **Ambidextrous**

HEALTH-RELATED QUESTIONS

12. Are you color-blind? **Yes** **No**
13. Do you have diabetes? **Yes** **No**
14. Is your vision corrected (glasses/contacts)? **Yes** **No**
Are you wearing them now? **Yes** **No**
15. Do you have severe visual impairments, such as cataracts or glaucoma? **Yes** **No**

16. Do you have any hearing loss (hearing aid)? **Yes No**
17. Have you ever or do you now have seizures? **Yes No**
18. Have you ever had a head injury (e.g., automobile accident, fall, sports injury)? **Yes No**
19. Have you ever been unconscious? **Yes No** If so, for how long? _____
20. Do you have any medical conditions? **Yes No** (please describe) _____
21. Do you have any neurological disorders? **Yes No**
22. Do you have a learning disability? **Yes No**
Has this been formally diagnosed? **Yes No** Diagnosis: _____
23. Have you ever received ECT treatment? **Yes No**
24. Have you ever received psychosurgery? **Yes No**
25. Do you smoke? **Yes No**
- a. Cigarettes? **Yes No**
 - b. Cigars / Pipes? **Yes No**
 - c. Chewing tobacco? **Yes No**
 - d. How many per day? _____
26. When you were born:
- a. Were you born full term? **Yes No Don't Know**
 - i. If premature, how many months was the pregnancy? _____
 - b. Were there any obstetric complications? **Yes No Don't Know**
 - c. Was your mother exposed to anything during her pregnancy (e.g., disease, toxins, alcohol, etc.)? **Yes No Don't Know**
 - d. Was your birth normal (e.g., head first, natural birth)? **Yes No Don't Know**
 - e. Did your mother smoke when she was pregnant? **Yes No Don't Know**

FAMILY HISTORY QUESTIONS

*Please complete these questions concerning your family. Please **DO NOT** list any specific names or identify any specific person in your answers.*

27. Does anyone in your family have a mental disorder? **Yes No**
28. Do you have any first degree relatives (e.g., mother, father, brother, child) with a mental disorder? **Yes No**
- a. What is the disorder?
 - i. Schizophrenia **Yes No**

- | | | | |
|------|---------------------------------|-----|----|
| ii. | Affective disorder | Yes | No |
| iii. | Alcoholism | Yes | No |
| iv. | Parkinsonism | Yes | No |
| v. | Movement disorder | Yes | No |
| vi. | Schizophrenia spectrum disorder | Yes | No |
| vii. | Other _____ | | |

29. Do you have any second degree relatives (e.g., aunt, uncle, grandmother, grandfather) with a mental disorder? **Yes No**

a. What is the disorder?

- | | | | |
|------|---------------------------------|-----|----|
| i. | Schizophrenia | Yes | No |
| ii. | Affective disorder | Yes | No |
| iii. | Alcoholism | Yes | No |
| iv. | Parkinsonism | Yes | No |
| v. | Movement disorder | Yes | No |
| vi. | Schizophrenia spectrum disorder | Yes | No |
| vii. | Other _____ | | |

30. Please list any medications you are currently taking

Current Medications	Dosage	Date Started
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

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