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Memory Profiles in Schizophrenia: A Neuropsychological Comparison with Temporal Lobe Epilepsy

S. Laura Lundy

S. Laura Lundy

Candidate

Psychology

Department

This dissertation is approved, and it is acceptable in quality and form for publication:

Approved by the Dissertation Committee:

Ronald A. Yeo, Ph.D. , Chairperson

Robert J. Thoma, Ph.D.

Derek Hamilton, Ph.D.

Steven Verney, Ph.D.

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by

S. LAURA LUNDY

B.S., Psychology, Duke University, 1998
M.S., Psychology, University of New Mexico, 2007

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ABSTRACT

Previous research has demonstrated various neuroanatomical and neuropsychological abnormalities in schizophrenia. Although results vary depending on population characteristics, medication status, imaging methodology, and choice of cognitive assessment measures, overall results suggest decreased cerebral volume within frontal and temporal lobes and in individual structures, particularly hippocampus, within these regions; abnormal connectivity within fronto-temporal networks; and deficits in executive function, working memory, processing speed, and memory, with verbal memory deficits more reliably demonstrated than non-verbal impairment. In particular, left-hemisphere hippocampal-dependent verbal memory impairments have been proposed to be a core feature of schizophrenia, as these deficits are reliably demonstrated in first-episode, medication-naïve patients, chronic in- and outpatients, and at-risk populations such as individuals with prodromal schizophrenia symptoms and first-degree relatives of patients with schizophrenia. Verbal memory deficits have also been reliably demonstrated in patients with left-hemisphere temporal lobe epilepsy (TLE), and those who have undergone temporal lobe resection (TLR). Given the known localization of structural abnormalities in TLR groups and their relation to deficits in memory, it seemed reasonable to compare memory and other neuropsychological functions in schizophrenia

and TLR groups to determine whether similar profiles emerged which might provide additional evidence of significant left-hemisphere involvement in the development and maintenance of schizophrenia. A comprehensive neuropsychological battery was administered to a total of 43 schizophrenia, left and right TLR, and control participants. Consistent with hypotheses, the schizophrenia and left TLR groups performed worse than controls on verbal memory, and the right TLR group performed worse than controls on non-verbal memory tasks, with a trend in the predicted direction for the schizophrenia group. Patients with schizophrenia also performed worse than controls on working memory, motor skills, and processing speed, as predicted. Hypotheses were not supported regarding overall memory profiles: the left and right TLR groups showed the expected interactive performance on verbal versus non-verbal memory, but the schizophrenia group was not found to have a memory profile similar to that of the left TLR group. Overall, results suggested that the cognitive profile of schizophrenia may best be represented as a complex interaction pattern rather than a hemisphere-specific model as seen in TLE.

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Introduction

Schizophrenia is classified as a psychotic disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000.). It is characterized by the presence of various combinations of emotional dysfunction, such as alogia, inappropriate affect, anhedonia, and impaired volition; perceptual abnormalities, such as delusions and hallucinations; thought and speech dysfunction, such as tangentiality, loose associations, and incoherence; disorganized behavior, such as hoarding useless objects or dressing inappropriately; and catatonic behavior, such as echolalia or posturing. In the majority of cases, schizophrenia is a chronic and severely debilitating disorder, impacting individuals' ability to obtain competitive employment, maintain social connections, and perform activities of daily living sufficiently to live independently. Given the severe nature of schizophrenic symptomatology and outcomes, it is not surprising that much research has been focused on elucidating the etiology, course, and nature of specific deficits in this disorder.

Neuroanatomical Abnormalities in Schizophrenia

Neuroimaging studies have consistently demonstrated neuroanatomical abnormalities in schizophrenia. Many brain regions, considered both as discrete areas and nodes within networks of interconnected structures, have been implicated. Depending upon the clinical characteristics (e.g., first-episode vs. chronic) of the population of study, some findings are more reliably demonstrated than others. Moreover, with the advent of magnetic resonance imaging (MRI), more subtle neuroanatomical differences can be observed than was previously possible with computed technology (CT) scanning (Seidman, Faraone, Goldstein, Goodman, Kremen, et al., 1999). Shenton and colleagues

(2001) recently published a review of 193 peer-reviewed magnetic resonance imaging (MRI) studies of structural abnormalities in schizophrenia. These reviews included studies of whole-brain, ventricular system, frontal lobe, temporal lobe, thalamus, and other brain regions. Of 50 studies of whole-brain volume, only 11 (22%) reported differences between patients with schizophrenia and healthy control subjects (e.g., Wright et al., 2000, in which patients were reported to have overall cerebral volume two percent smaller than controls); however, they did note that one study (Jacobsen, Giedd & Vaituzis, 1996) found smaller brain volumes in patients with childhood-onset schizophrenia, suggesting that reduced overall brain volume may be related to more severe genetic or environmental neurodevelopmental anomalies resulting in early onset of symptoms. In general, however, most MRI studies do not report differences in whole brain volume in schizophrenia versus healthy controls (e.g., McCarley, Wible, Frumin, Hirayasu, Levitt, et al., 1999).

Ventricular dilation is another finding commonly attributed to schizophrenia. Thirty-three MRI studies of the third ventricle were included in Shenton et al.'s (2001) review. Of these, 24 (73%) reported enlarged volume, which may be related to the reduction in thalamic volume inconsistently reported in schizophrenia, as these structures are located close to each other. Of five studies assessing the fourth ventricle, only one (20%) noted increased volume in schizophrenia. The clinical implications of enlarged fourth ventricle are unclear. The lateral ventricles have received much more attention in schizophrenia research, given their proximity to temporal lobe structures thought to play a central role in the development and maintenance of schizophrenic symptoms, and are discussed in the next section (see below).

The parietal lobe, although part of the heteromodal association cortex with interconnections to prefrontal and temporal lobe structures (Pearlson, Petty, Ross, & Tien, 1996) and associated with functions such as language and attention which are known to be impaired in schizophrenia (e.g., Bilder et al., 2000), has not been thoroughly studied with regard to schizophrenia. In their review, Shenton et al. (2001) only found 15 MRI studies of the parietal lobe, nine (60%) of which reported positive findings. Methodological differences among these studies may be partially responsible for discrepant findings, as methods of measurement vary (e.g., whole-lobe versus regional/functional subdivisions) and functional left-greater-than-right asymmetry, which is present in healthy brains and necessary for intact language development, has not always been evaluated. Nonetheless, some interesting relationships have been noted. Studies have shown a reversal of the normal left-greater-than-right ratio of angular gyrus (part of the inferior parietal lobule [IPL] particularly important for language comprehension) volume in male, but not female, patients with schizophrenia compared to controls (Frederikse, Lu, Aylward, Barta, Sharma, et al., 2000; Niznikiewicz, Donnino, McCarley, Nestor, Iosifescu, et al. 2000). One study also showed correlations between IPL and interconnected prefrontal (superior and inferior frontal gyrus and orbital gyrus) and temporal (anterior superior temporal gyrus [STG], amygdala, and hippocampus) cortices, providing evidence that the heteromodal association cortex may be affected in schizophrenia (Niznikiewicz et al. 2000).

The frontal lobes, including prefrontal cortex (PFC), are known to be essential for cognitive and behavioral regulation (Kolb & Whishaw, 2009) and have been fairly extensively researched regarding their roles in the development and/or maintenance of

schizophrenia. Shenton and colleagues (2001) reviewed 50 MRI studies of the anatomy of the frontal lobes in schizophrenia, of which 30 (60%) reported positive findings. However, it is important to note that most studies have measured the frontal lobe as one structure, rather than parceling out specific frontal and prefrontal regions, such as orbitofrontal and dorsolateral prefrontal cortices, which are known to have functionally different connectivities involved in various aspects of cognition. Thus, measurement of the entire frontal lobe may obscure more specific, localized differences. Nevertheless, results of studies of entire-lobe structure have suggested abnormalities in prefrontal-temporal connectivity. For example, in a study by Wible et al. (1995), no differences between male patients with schizophrenia (presenting with mainly positive symptoms) and male healthy controls were found in volume of PFC as a whole, but left prefrontal gray matter volume was found to correlate significantly with reduced volume of the left hippocampal-amygdala complex, left STG, and left parahippocampal complex in the schizophrenia group only. Breier et al. (1992) measured amygdala/hippocampus and PFC volumes in patients with chronic schizophrenia versus healthy controls. They found that patients had smaller right and left overall amygdala/hippocampal complex volumes as well as smaller right and left prefrontal volumes. Within the amygdala/hippocampal complex, they reported smaller right and left amygdala and left hippocampal volumes in the patient group. They further reported reduced prefrontal white matter in the patient group, with right-hemisphere prefrontal white matter highly correlated with right amygdala/hippocampal volume, suggesting the presence of abnormal corticolimbic connectivity in schizophrenia. Further evidence for abnormal prefrontal-limbic connectivity, particularly in the left hemisphere, in schizophrenia is suggested by a study

which reported a correlation between left hippocampal volume reduction and decreased cerebral blood flow to the dorsolateral (DL) PFC during an executive working memory task in the affected twin of monozygotic twins discordant for schizophrenia (Weinberger, Berman, Suddath, & Torrey, 1992).

Although few studies have measured subregions within the frontal lobe, those that have tended to report abnormalities in volume and connectivity as well. For example, Buchanan and colleagues (1998) divided the PFC into superior, inferior, middle, and orbital regions based on anatomical landmarks and found volumetric reductions of the right and left inferior prefrontal gray matter (primarily composed of Broca's area, which projects to DLPFC, STG, and other heteromodal areas which have been implicated in the pathogenesis of schizophrenia) in a mixed-gender sample of schizophrenia patients compared to controls. In a study conducted by Goldstein et al. (1999) comparing frontal lobe regions in patients with chronic schizophrenia to healthy controls, patients were found to have bilaterally reduced, though more so on the left, DLPFC areas, and reduced right orbitofrontal PFC area. Gur and colleagues (2000a) compared prefrontal volumes in a group of 29 neuroleptic-naive (16 men and 13 women) and 41 previously treated patients (24 men and 17 women) compared to healthy controls. They found DLPFC volume reductions of 9% in male patients and 11% in female patients, a dorsomedial PFC volume reduction of 9% in male patients only, and orbitofrontal volume reductions only in women (23% and 10% for lateral and medial regions, respectively). Importantly, when they compared the neuroleptic-naïve versus medicated patients, there were no significant differences in volume in any brain region, suggesting that PFC reductions are not simply a result of chronic medication. Other studies, however, have reported negative findings

regarding frontal lobe volumes, even when subregions were delineated and measured separately. For example, Baaré et al. (1999) evaluated left and right dorsolateral, medial, and orbital prefrontal gray and white matter volumes in patients with schizophrenia versus healthy controls. They reported no significant group differences in any region of interest (ROI), though they noted that volumes tended to be smaller in patients as a group. However, they did find significant correlations between reduced left and right prefrontal gray matter volume and performance on measures of verbal and visual memory in the patient group, suggesting that even in the absence of outright structural abnormalities, frontal lobe dysfunction likely contributes to the cognitive deficits seen in schizophrenia. In particular, this study highlights the association between dysfunction in PFC and memory functioning, which is known to be dependent on structures of the medial temporal lobe (Squire & Zola-Morgan, 1991).

Neuroanatomical Abnormalities in Temporal Lobe and Surrounding Areas

Fifty-five MRI studies of the lateral ventricular system were included in the Shenton et al. (2001) review; the lateral ventricles are considered important for schizophrenia research because they surround temporal lobe structures such as hippocampus and amygdala that have been implicated in impaired cognitive functioning in this group (see below). Of these 55 studies, 44 (80%) reported enlarged lateral ventricles in schizophrenia. For example, Andreasen et al. (1990) reported increased lateral ventricular volume in patients with schizophrenia, particularly in male participants. Lauriello et al. (1997) reported increased lateral and third ventricular volume in patients with chronic schizophrenia, regardless of gender. Kelsoe and colleagues (1988) found that lateral ventricular volume was increased by 62% in schizophrenic

subjects compared to healthy controls. Furthermore, of the 11 studies reviewed which did not report overall lateral ventricle enlargement, many noted enlargement in the temporal horn portion of the lateral ventricles, particularly in the left hemisphere. For example, Shenton and colleagues (1992) found that the volume of the left, but not right, lateral ventricle was enlarged in patients with schizophrenia, and that left temporal horn volumes were 180% larger, and the right temporal horn was 74% larger, in patients with schizophrenia than in healthy controls. In a study of first-episode schizophrenic patients, Bogerts et al. (1990) found that overall, patients had larger anterior temporal horn volumes than controls, and that female patients had larger left, but not right, total temporal horn volumes than controls. While findings of lateral ventricle enlargement are highly consistent in the schizophrenia literature, these abnormalities also occur frequently in other neurological disorder such as Parkinson's disease, Huntington's disease, and Alzheimer's dementia, and are thus not specific to the schizophrenia process (e.g., Apostolova et al., 2010). Nonetheless, enlargement of the ventricular space, especially in the left hemisphere, surrounding temporal lobe structures which have reliably been implicated in behavioral and cognitive dysfunction in schizophrenia suggests neurodevelopmental or neurodegenerative processes related to this region (Shenton et al., 2001).

The temporal lobe is comprised of two main divisions: lateral, or neocortical, and medial. The lateral temporal lobe structures include the STG (further broken down into the planum temporale and Heschl's gyrus, or transverse temporal gyrus), middle temporal gyrus, and inferior temporal gyrus. The medial temporal lobe structures include the hippocampus, amygdala, and parahippocampal gyrus (as well as the entorhinal cortex,

which is neuroanatomically continuous with the parahippocampal gyrus). Abnormalities in the temporal lobes have long been posited to be related to the behavioral and cognitive sequelae of schizophrenia [e.g., Kraepelin (1971), and Southard (1915), who believed that auditory hallucinations were the result of temporal lobe abnormalities]. Structural abnormalities in the temporal lobe and surrounding regions have been of particular interest in schizophrenia research, given the location of primary auditory cortex on Heschl's gyrus and the involvement of limbic system structures, and their connections to frontal and prefrontal cortex, in the formation of memory and language processing functions, which have been shown to be impaired in schizophrenia (e.g., Hoff et al., 1999). Shenton et al., (2001), for example, posited that hallucinations and cognitive deficits in schizophrenia are associated with abnormalities in medial temporal lobe structures (e.g., hippocampus, amygdala, and parahippocampal gyrus) involved in encoding and retrieval of memories. Lateral temporal lobe structures, such as the STG, have also been shown to be associated with hallucinations (e.g., Barta, Pearlson, Powers, Richards, & Tune, 1990; Penfield & Perot, 1963). It is not surprising, then, that much focus has been directed at investigating the dysmorphology and dysfunction of the temporal lobes in schizophrenia research.

In Shenton et al.'s (2001) review, 31 (61%) of the 51 MRI studies reporting whole-lobe volumes noted smaller overall temporal lobes in the schizophrenia compared to control group. For example, Bogerts and colleagues (1990) reported a 9% reduction in whole temporal lobe volume in male patients with first-episode schizophrenia compared to healthy controls, though no differences were noted in female subjects. Other studies have reported temporal lobe volume reductions only in the left hemisphere (e.g., Gur,

Cowell, Turetsky, Gallacher, Cannon, et al. 1998; Turetsky, Cowell, Gur, Grossman, Shtasel, et al., 1995), and in the left hemisphere only in male patients (e.g., Bryant, Buchanan, Vladar, Breier, & Rothman, 1999). Regarding lateral temporal lobe structures, most studies have focused on assessing the STG and its divisions. Overall, the majority of studies report volume reduction in schizophrenia. In fact, of the 12 MRI studies of gray matter volume in STG included in Shenton et al.'s (2001) review, 100% reported reduced volume (of 15 studies measuring STG gray and white matter, 10 [67%] reported positive findings). For example, Gur and colleagues (2000b) reported an 11.5% decrease in STG volume in males with schizophrenia, but not in females. Another study reported reduced STG gray matter in a heterogeneous (i.e., mixed-subtype) group of inpatients with chronic schizophrenia compared to healthy controls (Zipursky, Marsh, Lim, DeMent, Shear, et al., 1994). Holinger et al. (1999) investigated STG volumes in left-handed males with schizophrenia, and found that patients had bilaterally smaller gray matter volumes in the posterior STG (16% smaller on the right, 15% smaller on the left), and smaller total right STG than controls. This study highlights the importance of assessing handedness and hemispheric asymmetry in volumetric MRI research, as results may differ between left- and right-handed patients. The planum temporale (PT), another lateral temporal lobe structure important for language processing, has been investigated in schizophrenia research as well. A recent meta-analysis of PT volumes in schizophrenia concluded that although methodological differences in measurement likely obscured some results, strong evidence is nonetheless found for larger right PT in patients, resulting in a reversal of the developmentally-normal left-greater-than-right asymmetry in this region (Shapleske, Rossell, Woodruff, & David, 1999). In the Shenton et al. (2001) review, six of ten (60%)

studies of PT reported differences in asymmetry between patients and healthy controls (e.g., Barta, Pearlson, Brill, Royall, McGilchrist, et al., 1997; Petty, Barta, Pearlson, McGilchrist, Lewis, et al., 1995). Importantly, abnormalities in PT volume and asymmetry may be related to abnormalities in the heteromodal association cortex, which would strengthen the argument that frontal-parietal-temporal networks are disturbed in schizophrenia (Pearlson, Petty, Ross, & Tien, 1996).

In addition, much recent research has employed a voxel-based morphometry (VBM) approach to analyzing differences in cerebral volumes, in which concentration or density of gray matter (GM) is assessed relative to the concentration of other types of tissue within the brain. VBM has been hailed as a more reliable and unbiased method for analyzing volumetric differences in gray (GM) and white (WM) matter than conventional analyses of regions of interest (ROIs), as it utilizes an automated algorithm for mapping spatially normalized images from structural MRIs into standardized stereotactic space, thereby eliminating user error in delineation of ROIs and the bias inherent in specifying a priori ROIs rather than examining all regions as potentially significant (Segall et al., 2009). VBM studies tend to demonstrate significantly lower gray matter (GM) densities in schizophrenia-spectrum groups compared to healthy control groups, particularly in the temporal lobe. For example, in a recent meta-analysis of 15 studies which employed VBM analysis of brain tissue in schizophrenia, significant gray and white matter density differences were reported in 50 regions of interest (ROIs). One of the most consistent differences which emerged in the meta-analysis was within the left STG, which had a lower relative density in schizophrenia versus in healthy controls (Honea, Crow, Passingham, & Mackay, 2005). Interestingly, VBM studies have uncovered significant

differences in STG in schizophrenia-spectrum disorders that were not found using conventional ROI analysis (e.g., Giuliani, Calhoun, Pearlson, Francis, & Buchanan, 2005; Kubicki et al., 2002). Likewise, in a recent multisite VBM study, patients with schizophrenia-spectrum disorders (including schizophrenia, schizoaffective disorder, and schizophreniform disorder) were found to have a 5% reduction in GM density in the STG compared to healthy controls (Segall et al., 2009).

Structural abnormalities of the tissue of the medial temporal lobe are among the most robust neuroanatomical findings in schizophrenia research (Heckers, 2001). A number of MRI studies have reported smaller volume of the medial temporal lobe overall in schizophrenia (Bogerts et al., 1993; Gur et al., 2000b; McCarley et al., 1999; Wright et al., 2000), particularly in the left hemisphere (DeLisi et al., 1991; Shenton et al., 1992). In addition, VBM studies of schizophrenia have reported lower densities of gray matter in the medial temporal lobe overall compared to healthy controls. For example, in a meta-analysis conducted by Honea and colleagues (2005), nine of fourteen studies which assessed the temporal lobe reported reduced medial temporal lobe densities. Eight of these studies reported differences in the left hemisphere, with the remaining study (Wright et al., 1999) reporting a trend in this direction, while only three reported right-hemisphere differences.

As with the frontal lobe, however, parceling out the contributions of separate medial temporal lobe structures may be more informative for schizophrenia research than assessing the medial temporal lobe as a single unit. An important consideration in interpreting the results of studies of medial temporal lobe structure abnormalities is that although the hippocampus and amygdala are functionally different, they are

neuroanatomically continuous and it is somewhat difficult to reliably dissect these structures on MRI slices in order to evaluate their separate volumes. Thus many studies measure volumes of the hippocampal/amygdala complex as a whole, which may obscure more localized findings. Regardless, of the 49 studies included in Shenton et al.'s (2001) review which evaluated medial temporal lobe structures separately, 36 (74%) reported volume decreases in the hippocampal/amygdala complex, findings which are consistent with post-mortem results.

Recently, more studies have reported findings based on separate amygdala and hippocampus assessments. Some MRI studies have demonstrated reduced amygdala volume in schizophrenia bilaterally (e.g., Barta et al., 1997b; Breier et al., 1992; Jernigan et al., 1991; Marsh, Suddath, Higgins, & Weinberger, 1994), or unilaterally (e.g., left hemisphere: Barta, Pearlson, Powers, Richards, & Tune, 1990; right hemisphere: Pearlson et al., 1997), or only in males (Gur et al., 2000b). However, other studies have reported no differences in amygdala volume. A post-mortem study of amygdala volumes in schizophrenia versus healthy controls showed no significant difference bilaterally (Chance, Esiri, & Crow, 2002). MRI studies have also reported negative results. Studies of amygdala volume in first-episode patients (e.g., Niemann, Hammers, Coenen, Thron, & Klosterkötter, 2000), and in patients with chronic schizophrenia (e.g., Staal et al., 2000; Swayze, Andreasen, Alliger, Yuh, & Ehrhardt, 1992) have demonstrated no significant differences bilaterally. In contrast, studies of hippocampal volume in schizophrenia report differences more reliably. In Shenton and colleagues' (2001) review of MRI studies in schizophrenia, 17 of 25 studies (68%) which measured hippocampus separately from amygdala and other medial temporal lobe structures reported decreased

volume. VBM studies as well have demonstrated significantly reduced density of hippocampus in first-episode schizophrenia compared to both healthy control and patients with affective psychosis, particularly on the left (e.g., Kubicki et al., 2002; Rametti et al., 2007). However, while hippocampus abnormality is consistently found, the precise nature of the results has varied. Meta-analyses have posited that smaller hippocampus volume is equivalent across hemispheres (Nelson, Saykin, Flashman, & Riordan, 1998), even when limited to studies of first-episode patients (Steen, Mull, McClure, Hamer, & Lieberman, 2006). However, other first-episode studies have resulted in findings of significant left-less-than-right hippocampus asymmetry (Bogerts et al., 1990; Hirayasu et al., 1998). In a longitudinal study, Velakoulis et al. (2006) demonstrated hippocampus volume deficits bilaterally in chronic schizophrenia, in the left hemisphere only in first-episode schizophrenia, and not at all in schizophreniform psychosis.

It is also important to note that there have been scattered reports of null findings with regard to hippocampus volume in schizophrenia. For example, Marsh et al. (1997) reported no group difference in hippocampal volume in an inpatient sample with severe and chronic schizophrenia. Csernansky et al. (2002) reported significant abnormalities of hippocampal shape and asymmetry, but not overall volume after total cerebral volume was included as a covariate, in patients with schizophrenia in the residual stage. Because of the variability in group differences across reports, the etiological role of hippocampal anomaly in schizophrenia and its association with subsequent symptoms and course of the disorder remains a critical area for research (White et al., 2008).

Abnormalities in the cellular structure and neurochemistry of the hippocampus in patients with schizophrenia have also been reported in the literature. The *N*-methyl-d-

aspertate (NMDA) receptor system, and especially glutamate-mediated long-term potentiation (LTP), within the hippocampus has been shown to play a crucial role in normal learning and memory formation (Rezvani, 2006), though not necessarily in storage or retrieval of learned information (Constantine-Paton, 1994). Animal studies have demonstrated that administration of drugs which increase glutamatergic transmission enhance encoding of memories across multiple tasks, including spatial learning (e.g., Morris water maze and radial arm maze tasks) and olfactory discrimination tasks (Staubli, Rogers, & Lynch, 1994). In addition, studies with healthy human participants have shown that blockage of the NMDA receptor system with an antagonistic agent such as phencyclidine (PCP) or ketamine results not only in impaired learning and memory, but also in behavioral changes similar to the positive and negative symptoms of schizophrenia, making these viable analog studies for the investigation of impaired hippocampal functioning in schizophrenia (Jentsch & Roth, 1999; Lahti, Weiler, Michaelidis, Parwani, & Tamminga, 2001). For example, administration of ketamine (which has been utilized in studies rather than PCP due to its decreased potency and resulting neurotoxicity) resulted in impaired verbal working memory (Honey et al., 2004) and encoding and retrieval of episodic memory, dependent on frontal and hippocampal input (Honey et al., 2005) in fMRI studies with healthy controls.

Numerous postmortem neurochemical studies have found decreased glutamate receptor function, predominantly in the left hippocampus, in schizophrenia compared to healthy controls (e.g., Deakin et al., 1989; Harrison et al., 1991; Kerwin et al., 1988; Tsai et al., 1995). Other studies have reported excess glutamate (possibly related to decreased receptor functioning) in the temporal lobes of patients with schizophrenia (e.g., Cecil et

al., 1999). Magnetic resonance spectroscopy (MRS) has been employed in order to investigate relative concentrations of neurochemicals such as glutamate *in vivo* in schizophrenia. One study found a right-greater-than-left asymmetry in the ratio of glutamate, glutamine, and γ-aminobutyric acid (GABA), collectively denoted as Glx, to choline-containing compounds in the hippocampus of patients with schizophrenia compared to healthy controls, consistent with postmortem findings of glutamate deficit (Kegeles et al., 2000). Other MRS studies have demonstrated a relative increase in absolute glutamate concentration in the frontal and temporal lobes in schizophrenia as well. For example, van Elst and colleagues (2005) found increased glutamate concentration in the prefrontal cortex and hippocampus of patients with schizophrenia compared to healthy controls, and further reported that increased prefrontal cortex glutamate concentrations were correlated with poorer global mental functioning. However, results of MRS studies have been mixed. In a study by Ohrmann et al. (2005), patients with chronic schizophrenia were found to have lower levels of Glx in the dorsolateral prefrontal cortex than either healthy controls or first-episode patients. In a recent study by Bustillo et al (2011), Glx and other neurochemical levels were investigated in whole gray matter and whole white matter in patients with schizophrenia versus healthy controls, with subsequent investigation of several regions of interest including left and right frontal, parietal, and temporal gray matter. While concentrations of Glx were not found to differ between groups, lower Glx levels were found to correlate with impaired cognitive performance in the patient task only, on a neuropsychological test battery which included both verbal and nonverbal memory tasks. Thus, while research on glutamate levels and receptor functioning in schizophrenia is still limited,

results have demonstrated a link between abnormal functioning or concentration of glutamate receptors within the frontal and temporal lobes, including specific reports of hippocampus, and cognitive functioning in schizophrenia, warranting ongoing research.

As a whole, results of morphological evaluations of whole-brain and neuroanatomical subregions tend to suggest that volumetric abnormalities exist in multiple anatomical regions in schizophrenia, with some of the most consistent findings emerging for the temporal lobe and its component structures, particularly hippocampus and STG, as well as for frontal/prefrontal-temporal/limbic connectivities. Also of note, when unilateral differences are noted, they tend to be confined to the left hemisphere. The importance of decreased frontal and temporal tissue volume and impaired interconnectivity in schizophrenia is discussed in the following sections.

Neuropsychological Dysfunction

Schizophrenia has been shown to be associated with neuropsychological deficits across a wide range of domains, including memory, attention, executive function, motor skills, and processing speed (Bilder, 1996; Bilder et al., 2000; Braff et al., 1991; Goldberg & Gold, 1995; Pantelis, Nelson, & Barnes, 1996; Saykin et al., 1994). A generalized cognitive deficit has been theorized to exist in schizophrenia, such that domain-specific deficits are less pronounced in relation to an overall deficit (e.g, Blanchard & Neale, 1994; Dickinson & Harvey, 2008; Dickinson, Iannone, Wilk, & Gold, 2004; Dickinson, Ragland, Gold, & Gur, 2008; Heinrichs & Zakzanis, 1998; Mohamed, Paulsen, O'Leary, Arndt, & Andreasen, 1999; Saykin et al., 1994). Several meta-analyses have suggested that overall cognitive means in groups with schizophrenia are approximately one standard deviation below that of healthy control groups, with

individual variable means typically falling within one-third standard deviations above or below that level (e.g., Dickinson, Ramsey, & Gold, 2007; Heinrichs, 2005; Heinrichs & Zakzanis, 1998). Evidence of significant intercorrelation among neurocognitive domains is often cited as a main support for the theory of generalized cognitive deficit, and proponents theorize that the pattern of deficits represents a deficit in a general cognitive ability factor known as "g," (Dickinson, Ragland, Gold, & Gur, 2008). For example, Dickinson and colleagues (2008) reported that a single common ability factor accounted for 63% of the diagnosis-related variance in overall cognitive performance in their sample of mixed first-episode and chronic stable schizophrenia outpatients.

On the other hand, many studies have failed to demonstrate overall cognitive impairment in patients with schizophrenia using numerous different methodologies and assessment measures (e.g., Cohen, Barch, Carter, & Servan-Schreiber, 1999; Nuechterlein et al., 2004). Other researchers have suggested that there exist several consistent domain-specific deficits within a background of generalized cognitive deficits, as these domains tend to show disproportionately large deficits even after the effects of a general ability factor are considered. In particular, verbal memory, including immediate and delayed recall, free and cued recall, and recognition, is consistently impaired (Aleman, Hijman, de Haan, & Kahn, 1999; Dickinson, Ragland, Gold, & Gur, 2008; Heinrichs & Zakzanis, 1998; Hoff et al., 1999; Toulopoulou, Morris, Rabe-Hesketh, & Murray, 2003). Among verbal memory deficits, recall tends to be affected more than recognition (Clare, McKenna, Mortimer, & Baddeley, 1993; Hanlon et al., 2006; Johnson, Klinger, & Williams, 1977; Nacmani & Cohen, 1969). Episodic memory (memory for events) and semantic memory (memory for facts), which together are often

referred to as declarative memory, seem to be affected in patients with schizophrenia more than is procedural memory (Cirillo & Seidman, 2003; Clare, McKenna, Mortimer, & Baddeley, 1993; Goldberg et al., 1993; Gras-Vincendon et al., 1994; Kazes et al., 1999; McKenna et al., 1990; Tamlyn et al., 1992; Weiss and Heckers, 2001). Deficits in verbal memory have been shown to be present in both first-episode, nonmedicated patients (Mohamed et al., 1999; Riley et al., 2000; Saykin et al., 1994), in high-risk patients (i.e., with attenuated psychotic symptoms; Lencz et al., 2006) and in unaffected first-degree relatives of schizophrenic patients (Kremen et al., 1994; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Snitz, MacDonald, & Carter, 2006), leading many researchers to postulate that impaired verbal memory is a primary neuropsychological deficit and may represent a core feature of the disorder rather than an effect of chronicity or antipsychotic medication (Saykin et al., 1994).

Non-verbal memory has been less systematically evaluated in schizophrenia. Some studies have suggested that although memory for faces or designs may be impaired, the deficit is relatively small compared to verbal memory deficits (e.g., Saykin et al., 1991). Others have reported equally impaired immediate and delayed verbal and non-verbal memory deficits (e.g., Calev, Korin, Kugelmass, & Lerer, 1987; Gold et al., 1992b; Kolb & Whishaw, 1983). One study utilizing the Wechsler Memory Scale (Form 1) reported poorer performance on measures of immediate and delayed verbal, and delayed non-verbal, memory in schizophrenia compared to both healthy controls and a group with TLE (Seidman et al., 1998). Of note, these authors reported that although delayed free recall of designs was impaired, retention for this material was intact, suggesting that difficulties with initial encoding, rather than retrieval, of visual

information may be impaired in schizophrenia. Overall, deficits in visual memory are generally reported in schizophrenia, though the degree and nature of impairment vary considerably.

Declarative, episodic, and working memory have long been recognized as being dependent on the function of an intact hippocampus, which is necessary for encoding and consolidating new memories (Eichenbaum, Otto, & Cohen, 1994; Eichenbaum, Schoenbaum, Young, & Bunsey, 1996; Scoville & Milner, 1957; Wittenberg & Tsien, 2002). While research in the area of hippocampal structure and memory functions in schizophrenia is complicated by factors such as the heterogeneity of schizophrenia subject groups, medication effects, chronicity, and normally occurring gender-based and hemispheric neuroanatomical asymmetries, much research has been conducted which investigated this relationship in other neurologic conditions.

Relationship of Hippocampal Abnormality and Memory Function in Epilepsy

Numerous studies of memory processes in patients with hippocampal injury have demonstrated significant impairment, particularly in the epilepsy literature. Neuropsychological studies of patients with temporal lobe epilepsy (TLE) and patients who have undergone unilateral temporal lobe resection (TLR) show a fairly consistent pattern of verbal memory deficits in left hemisphere TLE and after left hemisphere TLR, and non-verbal memory deficits in right TLE and after right hemisphere TLR (Delaney, Rosen, Mattson, & Novelly, 1980; Giovagnoli, Casazza, & Avanzini, 1995; Ladavas, Umilta, & Provinciali, 1979; Majdan, Sziklas, & Jones-Gotman, 1996; Ojemann & Dodrill, 1985). However, resection of the temporal lobe in epilepsy is a complicated procedure which can result in memory impairment alone, or in a pattern of cognitive

deficits in multiple cognitive domains such as attention and language, depending on the amount and area of tissue excised. Surgical procedures differ widely, with anterior temporal lobectomy (ATL) still most commonly applied. In this procedure, approximately 4.5 cm of anterior temporal cortex, including STG, medial temporal gyrus, and inferior gyrus, are removed along with fusiform gyrus, parahippocampal gyrus, and hippocampus (Davies, Hermann, Dohan, Foley, Bush, et al., 1996). More recent advances in combining data of localized lesions on MRI scans with epileptogenic foci determined by electrophysiological monitoring have lead to an increase in tailored surgical approaches such as amygdalohippocampectomy (AH; Clusmann, Schramm, Kral, Helmstaedter, Ostertun, et al., 2002), in which approximately 2-3 centimeters of hippocampus, a large part of the amygdala, and the parahippocampal gyrus are removed. This procedure spares hippocampal tissue but leaves less amygdala tissue intact than ATL (Goldstein & Polkey, 1993). Some studies have shown that the extent of temporal tissue removed correlates with verbal deficits on the left and visual deficits on the right (e.g., Clusmann et al., 2002; Katz, Awad, Kongy, Chelune, Naugle, et al., 1989), however other studies have suggested that the extent of post-operative memory deficits depends more on pre-surgical performance than on surgical procedure (e.g., Goldstein & Polkey, 1993).

Other factors posited to have an effect on postsurgical outcomes include presence of hippocampal sclerosis and age of hippocampal insult. In a retrospective study of 20 subjects with TLE, Mathern, Pretorius, & Babb (1995) found that the presence and type of initial precipitating injury (i.e., medical illness/trauma versus idiopathic TLE) and the age of the patient when the injury occurred were significantly related to the pathological

findings in the hippocampus at time of surgery. Specifically, patients with a history of a significant initial precipitating injury that occurred prior to age 5 years were more likely to have unilateral hippocampal sclerosis on MR imaging than patients with initial injury after age 5 or with idiopathic TLE. Another study of 122 patients who had undergone ATL surgery examined the relationship between age of seizure onset, duration of epilepsy, and extent of hippocampal sclerosis (Davies et al., 1996). They found that the younger the age of seizure onset, and the longer the duration of epilepsy prior to ATL, the higher the extent of sclerosis. In a study by Hermann and colleagues (1995), although degree of hippocampal sclerosis was not assessed, both later age of seizure onset and older age at time of resection were significant and selective predictors of episodic memory decrease for left ATL patients. Overall, then, results from these studies suggest that early seizure onset and extended epilepsy duration are associated with the development of significant hippocampal sclerosis. In combination with results of studies such as that of Bell and Davies (1998), which suggest that patients without significant left hippocampal sclerosis who underwent left ATL were at higher risk for developing post-surgical deficits in verbal memory, it can be reasonably theorized that age of seizure onset may be inversely related to post-ATL verbal memory performance in patients with left-sided TLE. However, there are reports in the literature of no difference in post-surgical memory skills in patients with early versus late seizure onset (e.g., Vargha-Khadem, Gadian, Watkins, Connelly, Paesschen, et al., 1997). The inconsistent results of a small number of studies nevertheless highlight the importance of assessing age of seizure onset and duration of epilepsy when evaluating post-surgical memory functioning.

Spiers et al. (2001) investigated unilateral temporal lobectomy patients' visuo-spatial and episodic memory using a virtual-reality town to assess lateralized hippocampal function. To assess spatial memory, they evaluated patients' ability to navigate to certain locations, to recognize town scenes, and to do map reconstruction. To assess episodic memory, the participant collected different objects from different individuals (person) in different locations (place) in a certain order (time) and their recognition of these details was measured. Patients with right temporal lobectomy were impaired on the navigational measures compared to controls. In contrast, patients with left temporal lobectomy exhibited a deficit for the episodic memory measures. This study further illustrated a lateralized deficit for each version of the memory task and functionally dissociated the two hippocampi. However, other studies have shown that patients with unilateral hippocampal damage manifest allocentric spatial deficits, regardless of the hemisphere of damage (Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Maguire, Burke, Phillips, & Staunton, 1996) and that episodic memory function does not always lateralize to one hippocampus (Ryan et al., 2001; Viskontas, McAndrews, & Moscovitch, 2000). Therefore, it has not been clear whether episodic memory function is lateralized to left hippocampus and visuo-spatial memory to right hippocampus.

Thus, while a fairly consistent pattern of cognitive functioning, particularly in terms of memory skills, tends to emerge post-TLR, the results of most research paradigms must be considered with caution given differences in the duration, frequency, nature, and extent of pre-surgical seizure activity and resulting sclerotic processes, amount and site of tissue removal, and patients' pre-surgical functioning. Nonetheless,

these studies provide a foundation for investigating the relationship between hippocampal dysfunction and memory impairment in schizophrenia.

Relationship of Hippocampal Abnormality and Memory Function in Schizophrenia

Modern theories of the etiology of schizophrenia involve altered expression of multiple genes and neurodevelopmental processes (Censits, Ragland, Gur, & Gur, 1997; Rapoport, Addington, Frangou, & Psych, 2005) affecting the functions and connections of several brain areas, one of which is the hippocampus (Molina et al., 2002; Pantelis, Yücel, Wood, McGorry, & Velakoulis, 2003). Functional neuroimaging has linked hippocampus dysfunction to impaired performance on memory tasks in schizophrenia. In a positron emission tomography (PET) study, Heckers et al. (1998) identified lesser hippocampus activity in patients than controls during attempts to recall studied words. In a functional magnetic resonance imaging (fMRI) study, controls exhibited greater activation than patients in left anterior hippocampus during encoding and in hippocampus bilaterally during recognition (Jessen et al., 2003). Functional impairment related to the hippocampus extends to the ability to comprehend relationships and draw inferences, as demonstrated by a selective deficit in discrimination accuracy when cognitive flexibility is required, which has been observed in schizophrenia using fMRI (Öngur et al., 2006). Using a relational-memory task, Hanlon et al. (2005) directly assessed hippocampus activity with magnetoencephalography (MEG), reporting abnormal right hemisphere processing of nonverbal stimuli accompanied by a possibly compensatory, left-lateralized activation in schizophrenia.

The relationship of neuropsychological function to structural abnormality in the hippocampus remains unclear. With hippocampus critical for some aspects of memory, it

may play a central role in visual and verbal memory impairments exhibited in schizophrenia (Cirillo & Seidman, 2003; Saykin et al., 1991; 1994). Lack of a relationship between hippocampus volume and episodic memory in people with schizophrenia or controls has been reported by some studies (Bilder et al., 1995; DeLisi et al., 1991; Torres, Flashman, O'Leary, Swayze, & Andreasen, 1997). However, other studies have shown a positive relationship between hippocampus and memory function in schizophrenia. Gur et al. (2000b) found a positive correlation between gray matter volume of the hippocampus and episodic memory scores across patients and controls of both sexes. Studies by Saykin et al. (1991, 1994) have demonstrated a particularly large memory impairment, relative to attention and executive function deficits, in unmedicated patients with schizophrenia. They determined that impaired visual, and particularly verbal learning and memory, distinguished patients from normal controls better than other neuropsychological variables, and they related these deficits to those found after temporal-hippocampal damage. Gruzelier et al. (1988) administered a battery of neuropsychological tests to patients with schizophrenia and normal controls, also finding a generalized deficit, but with the most striking deficits again emerging on memory tasks involving temporal-hippocampal function.

Some researchers have posited that abnormalities in structure and function of the left hippocampus in particular may be related to memory deficits in schizophrenia. For example, Seidman et al. (2002) found that immediate and delayed verbal memory and left hippocampus volume were positively correlated in schizophrenia patients and in their relatives, as well as in controls, while no correlations emerged with the right hippocampus. Further, amygdala-anterior hippocampus volume was found to be

positively correlated with delayed verbal memory in relatives of patients with schizophrenia and controls (O'Driscoll et al., 2001). However, some investigations of structure-function relationships have found differential patterns of correlations between hippocampus volume and verbal IQ or verbal or visual memory in controls and people with schizophrenia (Kuroki et al., 2006; Sachdev, Brodaty, Cheang, & Cathcart, 2000; Sanfilipo et al., 2002; Toulopoulou et al., 2004). Findings of differential patterns of correlations for patients and controls are thought to indicate a loss of normal structure-function relationships, possibly arising from aberrant neurodevelopment.

Current Directions in Hippocampal Research in Schizophrenia

With some degree of hippocampal volume deficits in schizophrenia well established but the nature and mechanisms of its functional consequences unclear, attention is turning to localizing hippocampus volume decrements along the anterior-posterior axis. One study confirmed the presence of overall hippocampus volume deficits in schizophrenia but maintained that the loss was diffuse rather than topographically specific (Weiss et al., 2005). However, Narr et al. (2004) made a strong argument for factoring regional specificity into hippocampus measurements in a study that demonstrated volume deficits localized to midbody and anterior hippocampus in first-episode schizophrenia. Consistent with Narr et al.'s (2004) finding, smaller anterior hippocampus volumes have been observed in both first-episode and chronic schizophrenia (Lieberman et al., 2001; Pegues et al., 2003; Szeszko et al., 2003). Other studies have found deficits localized to posterior hippocampus in chronic schizophrenia (Narr et al., 2001) and in first-episode patients (Hirayasu et al., 1998).

One reason for discrepancies among volumetric studies may be that critical hippocampus subregions are not being discriminated, as few studies have combined neuropsychological assessment with hippocampus subregion measurements as discussed above. Anterior hippocampus volume deficits have been correlated with decrements in executive and motor function, but not memory, in first-episode schizophrenia (Bilder et al., 1995), with the effect present for men but not for women in a similar study (Szeszko et al., 2002). Given the substantial evidence for episodic memory dysfunction and hippocampus volume deficits in schizophrenia, Thoma et al. (2009) further investigated this relationship, taking subregional measurements into account. In this study of 24 patients with schizophrenia and 24 matched healthy controls, overall intracranial (ICV), white (WM) and gray (GM) matter, and anterior (AH) and posterior (PH) hippocampal volumes were assessed using magnetic resonance imaging (MRI). Memory was assessed using the Wechsler Memory Scale, Revised Edition (WMS-R) Logical Memory (LM) and Visual Reproduction (VR) subtests. Neuropsychological domains of intelligence (IQ), attention, and executive function were also evaluated with respect to volumetric measures. No group differences were found for ICV, GM, or WM. They found that neuropsychological performance was impaired overall and AH volume was smaller in the schizophrenia group. In the control group, verbal memory (WMS-R LM1 & LM2) scores correlated positively with right AH and left PH volumes. There were no significant brain-behavior correlations associated with visual memory (WMS-R VR1 & VR2) for the control group. In the schizophrenia group, the pattern of correlations was markedly different. LM1 was *negatively* correlated with right AH volume. VR1 and VR2 were also *negatively* correlated with right AH volume, and *positively* correlated with bilateral PH

volume. It should be noted that the results of this study were not consistent with the majority of the existing literature in terms of hippocampal volume correlations and with regard to hemispheric localization of memory (i.e., left hippocampus presumed to be more involved in verbal memory, and right hippocampus more involved with non-verbal memory).

The Current Study

Given the discrepancies in the existing research involving the complex relationship between hippocampus and memory in schizophrenia, specifically in terms of lateralization and anterior-posterior localization, further investigation is warranted to reliably discriminate differential functional patterns. The previously described study (Thoma et al., 2009), in conjunction with multiple reports in the literature suggesting that schizophrenia may best be characterized as a fronto-temporal, particularly left hippocampal, disorder (e.g., Kerwin, Patel, Meldrum, Czudek, & Reynolds, 1988; Seidman et al., 2002; Thoma et al. 2003; Hanlon et al. 2005) prompted the design of the current study.

The present study was designed to further investigate the theory that schizophrenia can be well-characterized by hippocampal dysfunction, particularly in the left hemisphere. To that end, we proposed to compare verbal and nonverbal memory in schizophrenia to VM and NVM in patients who had undergone unilateral temporal lobe resection (TLR) for medically intractable epilepsy, as the dissociation between verbal and nonverbal memory deficits by hemisphere in this group has been fairly consistently described in the literature (e.g., Ojemann & Dodrill, 1985; Lee et al., 2002; Richardson et al., 2004). In addition to verbal and nonverbal memory, the domains of attention

(encompassing working memory and processing speed), language processing, visuospatial processing, motor skills, and executive function were assessed using a thorough battery of neuropsychological tests. Based on results from neuroimaging and prior neuropsychological studies, the hypotheses were as follows:

1) Compared to the healthy control group, the schizophrenia and left TLR groups would perform worse on measures of immediate and delayed verbal memory.

2) Compared to the healthy control group, the schizophrenia and right TLR groups would perform worse on measures of immediate and delayed non-verbal memory.

3) The schizophrenia group would perform worse than the healthy control group on measures of executive function/attention, motor skills, working memory, and processing speed.

4) Overall, the memory profile of patients in the schizophrenia group would more closely resemble that of the left TLR patients than that of the right TLR patients.

Method

Participants

Eight patients with schizophrenia (all male) were recruited from the New Mexico Veteran's Administration Health Care System and from the University of New Mexico Health Sciences Center. All participants were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (First, Spitzer, Gibbon, & Williams, 1996). Participants with a history of alcohol or other substance abuse in the 3 months preceding the study were excluded. Other exclusion criteria included history of severe head trauma (i.e., injury with loss of consciousness longer than five minutes), neurological disorder, or unstable medical illness. All participants met predetermined criteria for clinical stability, that is, they had been treated with the same antipsychotic medications for at least 3 months and had not had an inpatient stay during the past year.

Twenty-one patients with medically intractable temporal lobe epilepsy (TLE) who underwent surgical unilateral temporal lobe, including hippocampus, resection for seizure control were also recruited. Thirteen patients were recruited from the University of New Mexico Hospital's Department of Neurosurgery, Clinical Epilepsy Program, and underwent neuropsychological testing by this author. Neuropsychological data from an additional nine patients with TLE was collected at the University of Washington Regional Epilepsy Center and provided by Dan Drane, Ph.D., a neuropsychologist currently on the faculty of the Emory University Department of Neurology. Thirteen participants (eight male, five female) had undergone left temporal lobe resection (TLR), and eight participants (five female, three male) had undergone right TLR. All patients were between one and two years post-surgery and had been seizure-free since the time of

surgery. Surgical details (i.e., volume of temporal lobe structures removed) were available for a small subset of these patients who were recruited from UNM and are presented in Table 1. All participants were assessed for lifetime history of psychiatric diagnoses using the SCID-CV, and individuals meeting lifetime criteria for any Axis I disorder were excluded. Participants in the left and right TLR groups were matched to the schizophrenia group on age and education where possible.

Table 1. Surgical Details for TLR Patients

Participant description	Surgical notes
Patient 1 (LTLR)	3.5 cm left temporal lobe removed
Patient 2 (LTLR)	4 cm left temporal lobe removed
Patient 3 (RTLR)	"at least 5 mm of posterior right hippocampus remains"
Patient 4 (LTLR)	5 cm left temporal lobe removed

Fourteen healthy comparison participants (12 male, 2 female) were recruited through advertisements in the local media. Participants in the control group were matched to the schizophrenia group by age and education where possible. Exclusion criteria included history of head injury, neurological disorder, or unstable medical illness. In addition, lifetime history of psychiatric diagnosis was assessed through the SCID-CV, and individuals meeting lifetime criteria for any Axis I disorder were excluded.

Demographic information for each group (schizophrenia, left TLR, right TLR, and control) is given in Table 2. All participants were right-handed by self-report. In order to determine whether groups were comparable in terms of demographic variables, the means for age, education, degree of right-handedness (Waterloo Handedness

Table 2. Demographic Data by Group

	SCZ (n = 8)		LTLR (n = 13)		RTLR (n = 8)		NC (n = 14)	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age (years)	37.63	8.86	35.31	11.88	34.38	8.67	31.86	6.70
Education (years)*	13.38[b]	2.20	13.23[a]	3.00	12.38[a]	1.77	15.34[b]	1.60
	(n = 8)		(n = 5)		(n = 4)		(n = 14)	
Age at sz onset	n/a	n/a	17.00	10.76	18.08	12.52	n/a	n/a
Epilepsy duration	n/a	n/a	23.40	15.76	18.25	17.86	n/a	n/a
	(n = 8)		(n = 8)		(n = 4)		(n = 14)	
WHQ Total	139.13	9.92	141.50	12.74	142.50	7.05	131.50	13.15
HISP*	55.00[a]	14.60	45.25[a,b]	24.31	74.67[a,d]	2.31	37.21[b]	16.18
HISP-Parent	30.38	22.68	40.13	23.07	57.00	21.66	28.62	17.28
	(n = 8)		(n = 13)		(n = 8)		(n = 14)	
	%	*(N)*	*%*	*(N)*	*%*	*(N)*	*%*	*(N)*
Female	0.00	(0)	38.5	(5)	62.5	(5)	14.3	(2)
Caucasian	50.0	(4)	69.2	(9)	75.0	(6)	57.1	(8)
Hispanic	37.5	(3)	15.4	(2)	25.0	(2)	28.6	(4)
Native American	0.0	(0)	15.4	(2)	0.0	(0)	0.0	(0)
Asian	0.0	(0)	0.0	(0)	0.0	(0)	14.03	(2)
Indian	12.5	(1)	0.0	(0)	0.0	(0)	0.0	(0)

Note. SCZ = Schizophrenia group; LTLR = Left temporal lobe resection group; RTLR = Right temporal lobe resection group; NC = Normal control group; sz = seizure; WHQ = Waterloo Handedness Questionnaire; HISP = Hollingshead Index of Social Position.

*ANOVA p <.05. Groups with different superscripts differ at the p <.05 level.

Questionnaire [WHQ] total score), participant socioeconomic status (SES), and parental SES (measured by Hollingshead Index of Social Position Scale [HISP], Hollingshead, 1957; see Appendix A) were tested as dependent variables in a series of univariate ANOVAS with group membership as the independent variable. Differences between groups were significant for years of education [$F(3,39) = 3.08$, $p < .05$] and participant SES [$F(3,29) = 4.46$, $p < .05$]. Planned contrasts were conducted to determine the directionality of these results. Regarding education, the control group had significantly more years of education than the left TLR [$t(39) = 2.20$, $p < .05$] and right TLR [$t(39) = 2.77$, $p < .01$] groups. There were no significant differences in educational level between the schizophrenia and either left or right TLR groups. In terms of SES, the control group had significantly lower scores, and therefore higher SES, than the schizophrenia [$t(29) = -2.27$, $p < .05$] and right TLR [$t(29) = -3.33$, $p < .01$] groups, while the left TLR group had significantly lower scores/higher SES than the right TLR group [$t(29) = -2.46$, $p < .05$]. There were no significant differences in mean age or overall parent SES.

Demographic Instruments

Demographic Questionnaire (Appendix A). A short questionnaire established participants' age, years of education, ethnicity, and primary language. For the TLR groups, date of resection surgery was also established.

Hollingshead Index of Social Position Scale (HISP; Hollingshead, 1957; Appendix B) Socioeconomic status (SES) was assessed with the Hollingshead ISP (Hollingshead, 1957), a brief assessment of social class position obtained from self-reported occupational and educational status. Occupation is ranked on a 1 (executive) to 7 (unskilled employee) scale, and education is ranked on a 1 (professional degree) to 7 (less

than 7 years of school) scale. To calculate ISP, the ranking on the occupation scale is multiplied by 7, and the ranking on the education scale is multiplied by 4. These numbers are then added to determine the final ISP score, such that higher numbers represent lower SES. For the current study, information was obtained for the participant and both of his or her parents. For purposes of data analysis, parent SES was reported as the lower of the two possible parent ISP scores.

Diagnostic and Symptom Inventory Instruments

Structured Clinical Interview for DSM-IV – Clinician Version (SCID-CV; First, Spitzer, Gibbon, & Williams, 1996). The SCID is a semi-structured interview with a format that corresponds directly to the diagnostic criteria in the DSM-IV, thus providing the necessary information to make appropriate diagnoses. The SCID is broken down into a number of modules; for this study, the overview and modules A (Mood episodes), B (Psychotic and associated symptom), C (Differential diagnosis of psychotic disorders), D (Mood disorders), E (Alcohol and other substance use disorders), and F (Anxiety and other disorders) were administered.

Beck Depression Inventory, Second Edition (BDI-II; Beck, Steer, & Brown, 1996; Appendix C). Studies have shown that comorbid depression affects a variety of neuropsychological test scores, often more so than would be seen with a single diagnosis (e.g., Moritz et al., 2001; Purcell, Maruff, Kyrios, & Pantelis, 1998). It is therefore important to assess depressive symptoms in neuropsychological studies. The BDI-II is a widely used self-report scale consisting of 21 categories of depressive symptoms (e.g., "Loss of Pleasure"). Each category is followed by four statements, arranged in a Likert-type scale from 0 to 3, with higher scores indicating more depressive symptomatology.

For the example noted above, the extreme responses are: “I get as much pleasure as I ever did from the things I enjoy,” (score of 0); and “I can’t get any pleasure from the things I used to enjoy,” (score of 3). The BDI-II has demonstrated acceptable validity and reliability in clinical (Chemerinski, Bowie, Anderson, & Harvey, 2008) and nonclinical (Storch, Roberti, & Roth, 2004) samples. Measures of the internal consistency of the BDI-II range from .91 to .93 in college students, and the BDI-II correlates .93 with the BDI, providing evidence for its convergent validity (Beck, Steer, & Brown, 1996; Dozois, Dobson, & Anhberg, 1998).

Magical Ideation Scale (MIS; Eckblad & Chapman, 1983; Appendix D). The Magical Ideation scale is a 30-item true/false questionnaire that includes items such as “I have felt that I might cause something to happen just by thinking too much about it,” (keyed “true”), and “I have never had the feeling that certain thoughts of mine really belonged to someone else,” (keyed “false”). Scores on the MIS range from 0 to 30, with higher scores indicating more pronounced magical thinking.

Revised Social Anhedonia Scale (RSAS; Eckblad, Chapman, Chapman, & Mishlove., 1982; Appendix E). The RSAS is a self-report true/false questionnaire consisting of 40 items concerning asociality and indifference to others, assessed by measuring interpersonal pleasures. The RSAS includes items such as, “Having close friends is not as important as many people say,” (keyed true), and “I feel pleased and gratified as I learn more and more about the emotional life of my friends,” (keyed false). Higher total scores on these scales indicate a lower capacity to feel pleasure, and thus greater levels of anhedonia.

Neuropsychological Measures

Wechsler Adult Intelligence Scale, Third Edition (WAIS-III; Wechsler, 1997). The WAIS-III is a widely used measure of overall intellectual ability. It is broken down into 14 subtests: Vocabulary, Similarities, Information, Comprehension, Arithmetic, Digit Span, Letter-Number Sequencing, Picture Completion, Block Design, Matrix Reasoning, Picture Arrangement, Digit-Symbol Coding, Symbol Search, and Object Assembly. Different combinations of subtests contribute to the Full Scale Intelligence Quotient (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ), and to indices of Verbal Comprehension (VCI), Perceptual Organization (POI), Working Memory (WMI), and Processing Speed (PSI). Raw scores on each subtest are converted to age-corrected scaled scores (mean = 10, standard deviation = 3). Overall indices are computed from the sum of the scaled scores of the appropriate subtests, and are expressed in standard scores (mean = 100, standard deviation = 15). Vocabulary (FSIQ, VIQ, and VCI) is a measure of expressive language skills in which the participant is asked to define single words. Similarities (FSIQ, VIQ, and VCI) is a measure of verbal abstract reasoning in which participants are asked to describe how two seemingly dissimilar items (e.g., eye and ear) are alike. Information (FSIQ, VIQ, and VCI) is a measure of general fund of knowledge (e.g., "In what country did the Olympic games originate?"). Arithmetic (FSIQ, VIQ, and WMI) is a time-limited measure of mental calculation in which participants are read word problems aloud and asked to provide the correct answer. Digit Span (FSIQ, VIQ, and WMI) is a measure of auditory attention and is comprised of two parts: Digit Span Forward, in which participants are asked to repeat a series of numbers, and Digit Span Backward, in which participants are asked to repeat a series of numbers in reverse.

Letter-Number Sequencing (FSIQ, VIQ, and WMI) is a measure of sequencing ability in which participants are asked to recall and sequence numbers and letters presented in an unordered format. Picture Completion (FSIQ, PIQ, and POI) is a timed measure of attention to essential visual detail in which participants are asked to identify what is missing from pictures. Block Design (FSIQ, PIQ and POI) is a measure of speeded constructional skills in which participants are asked to reconstruct 2x2 and 3x3 pictured designs using colored blocks. Matrix Reasoning (FSIQ, PIQ, and POI) is a measure of pattern analysis and non-verbal abstract reasoning in which participants are asked to extrapolate from a visual pattern or design and choose the design which completes the pattern. Digit-Symbol Coding (FSIQ, PIQ, and PSI) is a measure of efficiency in matching and reproduction of symbols associated with numbers. Symbol Search (FSIQ, PIQ, and PSI) is a measure of speeded symbolic information identification (Kaufman & Lichtenberger, 1999). In the current study, the subtests Comprehension, Picture Arrangement, and Object Assembly were not administered.

Wechsler Memory Scale, Third Edition (WMS-III; Wechsler, 1997). The WMS-III is a widely used measure of auditory and visual memory skills. In the current study, the following subtests were administered: Logical Memory I & II, Faces I & II, Verbal Paired Associates I & II, Mental Control, and Visual Reproduction I & II. Raw scores for each subtest are converted to age-adjusted scaled scores. Logical Memory is a measure of memory for contextual verbal information (paragraph-length short stories). Two stories are read to participants; the first story is read and participants are asked to repeat the story details immediately after its presentation. The second story is then read, with immediate recall, followed by a second presentation and recall trial, providing a measure of verbal

learning (learning slope). Approximately 30 minutes later, a delayed recall trial is administered, followed by a yes/no recognition trial for story elements (e.g., "Was the woman's name Anna Thompson?"). Faces is a measure of visual memory in which participants are shown a series of human faces and asked to identify them from a larger group of faces presented immediately afterward. A delayed recognition trial is administered 30 minutes later. Verbal Paired Associates is a measure of auditory associative memory in which participants are asked to learn eight word-pairs (e.g., "insect-acorn") over four trials. Participants are given corrective feedback after each trial in order to facilitate learning. A delayed recall trial (without corrective feedback) is administered 30 minutes later, followed by a yes/no recognition trial in which the eight target word-pairs are presented intermixed with novel word-pairs. Visual Reproduction is a measure of visual memory for a series of geometric designs. Participants are presented with five designs, one at a time, for ten seconds, then immediately asked to draw the figures. A delayed recall trial is administered 30 minutes later, followed by a yes/no recognition trial. Mental Control is a measure of attention, processing speed, working memory, and simple set-shifting in which participants are asked to recite sequences of numbers, letters, and months as quickly as they can, both forward and in reverse. The last item assesses set-shifting, as participants are asked to count by 6, starting with 0, and after every number, say a day of the week starting with Sunday (i.e., 0/Sunday, 6/Monday, etc.).

California Verbal Learning Test, Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000). The CVLT-II is a verbal memory test in which participants are asked to recall a 16-item word list over five learning trials. The words are presented in an

intermixed order, but can be mentally arranged into four semantic categories (furniture, vegetables, ways of traveling, and animals). Short-delay free and semantically-cued recall trials are administered following presentation and immediate free recall of a 16-item distracter list (List B). Long-delay free and semantically-cued trials are administered 20 minutes later, followed by a yes/no recognition trial consisting of target words, List B words, semantically-related distracter words, and unrelated distracter words. Outcome measures include total correct responses for learning trials 1-5, number of correct words recalled from List B, short- and long-delay free and cued recall number correct, and number of "hits" (true positives) and false positive errors on recognition. All raw scores are converted to z-scores (mean = 0.0, standard deviation = 1), except Trials 1-5 Total, which is expressed as a T-score.

Connors's Continuous Performance Test, Second Edition (CPT-II; Connors & Multi-Health Systems, 2000). The CPT-II is a widely used computerized measure of sustained visual attention. Participants are seated in front of a computer and told that they will see capital letters flash one at a time in the middle of the screen. They are instructed to press the space bar as quickly as they can whenever they see a letter, with the exception of the letter "X." They are instructed not to respond when they see the letter "X." The letters flash at interstimulus intervals of 1, 2, or 4 seconds with a display time of 250 ms. Multiple output variables are obtained from the CPT-II, including number of omission and commission errors, hit reaction time, variability, perseverations, detectability, and response style. Raw scores for each variable are converted to age-corrected T-scores.

Controlled Oral Word Association Test (COWA; Benton & Hamsher, 1989; Strauss, Sherman, & Spreen, 2006). This easily administered test of verbal fluency requires the participant to name, during a 60-second time limit, as many words as possible that begin with certain letters. Proper nouns, numbers, and words that only differ in suffix (e.g., "eat" and "eating") must be excluded. The most commonly used letters are F, A, and S. Following the phonemic fluency test, participants were asked to name as many animals as they could in 60 seconds to assess semantic fluency. Outcome measures included total correct responses, intrusive errors, and perseverative errors (repetitions). The raw score for total correct is compared to demographically-matched norms (based on gender, ethnicity [Caucasian or African-American], age, and education) to give a T-score (Heaton, Miller, Taylor, & Grant, 2004).

Ruff Figural Fluency Test (RFFT; Ruff, Light & Evans, 1987). The RFFT consists of five sheets of paper on which are arranged 40 squares containing a pattern of dots. Sheets 2 and 3 contain interference patterns as well as dots (in the same positions as on sheet 1), and sheets 4 and 5 have dot patterns that differ from sheet 1 and from each other. Each sheet also has a three-square practice page. Participants were instructed that they would have one minute (per sheet) to connect any two or more dots in each square to produce as many different patterns as they could. The test is scored for number of unique patterns and perseverations. Raw scores for total unique designs and the error score are converted to T-scores, and raw scores for total perseverative errors are converted to z-scores.

Trail Making Test, Parts A & B (TMT; Reitan & Wolfson, 1985). The TMT is an easily administered test of psychomotor speed, attention, and set-shifting. In Part A,

participants must connect 25 numbered circles in consecutive order as quickly as possible (giving measures of attention and psychomotor speed). In Part B, participants must connect 25 consecutively numbered and lettered circles by alternating numbers with letters as quickly as possible (adding a measure of set-shifting ability). Raw scores (number of seconds to completion) are expressed as demographically-corrected T-scores (Heaton, Miller, Taylor, & Grant, 2004).

Halstead Finger Tapping Test (FTT; Halstead, 1947). The Finger Tapping Test is a measure of simple bilateral finger motor speed in which participants were asked to depress a lever using their index finger, keeping the rest of their fingers and palm flat on the board, as quickly as they could for ten-second intervals. Five consecutive trials with total number of taps within five points of each other were required for each hand. Participants began with their dominant hand, and were given short breaks between each trial, with a full one-minute break after every three trials. The score is the average of the five trials for each hand, and is expressed as a demographically-corrected T-score (Heaton, Miller, Taylor, & Grant, 2004).

Grooved Pegboard (GP; Lafayette Instruments, 1989). The Grooved Pegboard test provides a measure of bilateral fine motor coordination and manual dexterity. Participants were asked to place 25 asymmetrically-shaped pegs from a large receptacle into 25 similarly-shaped holes arranged in five rows of five on the pegboard. They were told to pick up one peg at a time, and for the right hand, to work left to right, and for the left hand, to work right to left to fill in all the holes as quickly as possible. The outcome measure is the number of seconds to complete 25 holes for each hand. Raw scores are

converted to demographically-corrected T-scores (Heaton, Miller, Taylor, & Grant, 2004).

Auditory Consonant Trigrams (ACT; Brown, 1958; Peterson & Peterson, 1959). ACT is a measure of working memory in which participants are asked to recall a series of letters after an interference delay task. A screening section was administered prior to the working memory task: a consonant trigram (e.g., QLX) was presented orally to participants and they were asked to repeat the trigram immediately. Following five screening trials, participants were told that they would next hear three letters followed by a number. When they heard the number, they were instructed to begin counting backward, out loud, by threes, from this number, for interval delays of 3, 9, or 18 seconds (the examiner would say "stop" at the appropriate time), and then recite the three letters. Five trials each of 3-, 9-, and 18-second delays were administered. The outcome variables were total number of correctly recalled letters (regardless of order recalled) for each delay interval, plus total number of correctly recalled letters. Raw scores for each interval delay were converted to z-scores (Strauss, Sherman, & Spreen, 2006).

Boston Naming Test, Second Edition (BNT-2; Kaplan, Goodglass, & Weintraub, 1983). The BNT-2 is a widely used measure of one-word expressive vocabulary skills. Participants were shown line drawings of 60 items and asked to identify each word (e.g., hammock, compass). If the picture was obviously misperceived, a semantic cue was given (e.g., for item #45 "unicorn," the semantic cue is "a mythical animal"). If the participant was unable to provide the correct response either after 20 seconds with no cue or after presentation of the semantic cue, a phonemic cue was provided (e.g., "it starts with un-" for "unicorn"). The score is comprised of total number of correct responses

spontaneously given (i.e., with no cue) plus number of correct responses given following a semantic cue. Raw scores were converted into demographically-corrected T-scores (Heaton, Miller, Taylor, & Grant, 2004).

Waterloo Handedness Questionnaire (WHQ; Bryden, 1977; Appendix F). The WHQ is a 32-item self-report questionnaire which measures degree of right-handedness. Participants were asked to indicate which hand they would use to perform a series of unimanual activities (such as using a hammer or writing). Some of the items on the questionnaire reflect skilled performance (i.e., writing), whereas other items reflect relatively unskilled activities (i.e., opening a drawer). Five possible responses were offered for each question, allowing the participant to rate the frequency with which they would use a particular hand for each activity using a 5-point scale (i.e., 1 = "left always," 2 = "left usually," 3 = "left and right equally," 4 = "right usually," and 5 = "right always"). The outcome handedness measure was calculated as the total composite score of these individual responses. Higher scores correspond to a higher degree of right-handedness (i.e., scores below 96 would indicate increasing degrees of left-handedness, a score of 96 would indicate ambidextrousness, and scores above 96 would indicate increasing degrees of right-handedness).

Procedure

For the participants recruited from the NMVAMC and UNMH/UNMHSC and tested by this author, pilot data (MRI, MEG, and neuropsychological measures) were collected from each participant at three separate times. In the screening phase, participants were administered the SCID-CV to determine eligibility and diagnoses after providing written informed consent and agreeing to Health Insurance Portability and

Accountability Act policies. Participants were compensated upon completion of the screening process.

Once participants had been enrolled in the study and assigned group membership, neuroimaging and neuropsychological data were collected in separate sessions within two weeks of the initial interview. Neuroimaging results are reported elsewhere; only the results of the neuropsychological testing are reported here. Participants were compensated upon completion of each session (see Appendix K).

The neuropsychological test battery administered by the author included the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III); Wechsler Memory Scale, Third Edition (WMS-III; Logical Memory, Faces, Verbal Paired-Associates, and Visual Reproduction subtests); California Verbal Learning Test, Second Edition (CVLT-II); Grooved Pegboard (GP); Finger Tapping Test (FTT); Controlled Oral Word Association Test (COWAT; FAS and Animals); Auditory Consonant Trigrams (ACT); Trail Making Test, Parts A & B (TMT); Boston Naming Test, Second Edition (BNT-2); Ruff Figural Fluency Test (RFFT); and Connor's Continuous Performance Test, Second Edition (CPT-2). The Waterloo Handedness Questionnaire (WHQ) was administered to determine handedness. The neuropsychological measures were administered in random order in an effort to minimize order effects. In addition to neuropsychological measures, several self-report inventories of emotional functioning and current symptomatology were administered. These included the Beck Depression Inventory, Second Edition (BDI-II); the Revised Social Anhedonia Scale (RSAS); the Magical Ideation Scale (MIS). Upon completion of the neuropsychological battery, all participants were provided compensation in the form of payment of $50. The neuropsychological battery

administered to the Emory University participants was identical, except the following measures were omitted: CPT-2, ACT, BDI-II, MIS, and RSAS. In addition, different versions of two neuropsychological tests were given. The Delis-Kaplan Executive Function System (DKEFS) Trail Making Test and Design Fluency tests were given in place of the Trail Making Test and RFFT. For the DKEFS Trail Making Test, Condition 2 (Number Sequencing) is similar to Trails A and Condition 4 (Number-Letter Sequencing) is similar to Trails B. Although different normative data is used, standard scores are calculated which can be reliably compared across the different measures, thus data from the DKEFS TMT is included in the current study. The DKEFS Design Fluency test is administered differently than the RFFT, thus data from the DKEFS version is not included in the results presented here.

Testing by this author took place at the UNM Department of Psychiatry's Center for Neuropsychological Services over a three- to four-hour period in one day. One participant required a second session to complete the testing due to time constraints on the initially scheduled day.

Results

Descriptive Statistics

Information about general psychological functioning and overall intellectual ability for each group is given in Table 3. In order to determine whether groups were comparable in terms of general psychological and emotional functioning, as well as overall intelligence, the means for BDI-II, MIS, RSAS, and WAIS-III FSIQ were tested as dependent variables in a series of univariate analyses of variance (ANOVA) with group membership as the independent variable. No significant differences were found for FSIQ, indicating that all groups were comparable on overall intelligence. Importantly, FSIQ for all groups fell within the average range. On emotional measures, differences between groups were significant for RSAS only [$F(3,28) = 3.88$, $p < .05$]. Planned contrasts were conducted to determine the directionality of these results. There were no differences in scores among the experimental groups, but the schizophrenia [$t(28) = -2.32$, $p < .05$] and left TLR [$t(28) = -3.20$, $p < .01$] groups both had higher scores, indicating greater levels of social anhedonia, than the control group.

Neuropsychological Test Battery

To simplify analyses given the large number of individual outcome variables, standardized scores (mean = 0, standard deviation = 1) were calculated for each test, and combined to create neuropsychological composite scores (see Table 4). The Verbal Memory (VM) composite was created by averaging the WMS-III Logical Memory (LM), WMS-III Verbal Paired Associates (VPA), and CVLT-II subscale scores. The Nonverbal Memory (NVM) composite was created by averaging the WMS-III Faces and WMS-III Visual Reproduction (VR) subscale scores. The Executive Attention (EA) composite was

Table 3. Emotional/Symptom and Overall Intellectual Functioning Data by Group

	SCZ (n = 8)		LTLR (n = 8)		RTLR (n = 4)		NC (n = 14)	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
FSIQ	97.50	17.94	95.69	17.03	90.38	9.38	108.60	13.66
BDI-II	7.00	5.56	5.88	4.79	5.25	3.30	6.57	3.44
	(n = 8)		(n = 8)		(n = 3)		(n = 13)	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
MIS	10.00	7.72	10.88	4.97	14.33	5.77	8.69	7.17
RSAS*	$7.88^{a,b}$	6.10	$9.63^{a,b}$	5.26	$6.00^{a,c}$	1.73	3.23^{c}	2.80

Note. SCZ = Schizophrenia group; LTLR = Left temporal lobe resection group; RTLR = Right temporal lobe resection group; NC = Normal control group; FSIQ = Wechsler Adult Intelligence Scale, Third Edition, Full Scale Intelligence Quotient; BDI-II = Beck Depression Inventory, Second Edition; MIS = Magical Ideation Scale; RSAS = Revised Social Anhedonia Scale. *ANOVA p <.05. Groups with different superscripts differ at the p <.05 level.

Table 4. Individual Variables within Neuropsychological Composite Factors and Their Abbreviations

Composite Factor	Measures Included	Individual Variables Included
Verbal Memory (VM)	WMS-III: LM	Immediate Recall (LM1); Delayed Recall (LM2); Recognition (LMrec); Percent Retention (LM%)
	WMS-III: VPA	Immediate Recall (VPA1); Delayed Recall (VPA2); Recognition (VPArec); Percent Retention (VPA%)
	CVLT-II:	Trials 1-5 Total (CVLT1-5); List B Total (ListB); Short-Delay Free Recall (SDFR); Short-Delay Cued Recall (SDCR); Long-Delay Free Recall (LDFR); Long-Delay Cued Recall (LDCR); Recognition Hits (CVLTHits); Recognition False Positives (CVLTFP)
Nonverbal Memory (NVM)	WMS-III: Faces	Immediate Recognition (Faces1); Delayed Recognition (Faces2); Percent Retention (Faces%)
	WMS-III: VR	Immediate Recall (VR1); Delayed Recall (VR2); Recognition (VR-rec); Percent Retention (VR%)
Executive Attention (EA)	WMS-III:	Mental Control (MC)
	TMT:	Part B
	RFFT:	Perseverative Errors (PE)
	CPT-II:	Omission Errors (OE); Commission Errors (CE); Hit Reaction Time (HRT); Variability (V); Detectability (d'); Response Style (β); Perseverations (P); Hit Reaction Time Block Change (BC); Hit Reaction Time Inter-stimulus Interval Change (ISI)
Working Memory (WM)	WAIS-III:	Arithmetic (Arith); Digit Span (DS); Letter-Number Sequencing (LNS)
	ACT:	9-second (9); 18-second (18); 36-second (36)
Processing Speed (PS)	WAIS-III:	Digit-Symbol Coding (DSC); Symbol Search (SS)
	TMT:	Part A

Table 4 (cont.)

Composite Factor	Measures Included	Individual Variables Included
General Language (GL)	WAIS-III:	Vocabulary (Vocab); Similarities (Sim); Information (Info)
	COWA:	FAS (FAS); Animals (Animals)
	BNT-2:	Total Uncued & Semantically-Cued Correct (BNT)
Visuospatial Processing (VSP)	WAIS-III:	Picture Completion (PC); Block Design (BD); Matrix Reasoning (MR)
	RFFT:	Unique Designs (UD); Error Ratio (ER)
Motor Skills (MS)	GP:	Dominant Hand & Non-dominant Hand (GP)
	FTT:	Dominant Hand & Non-dominant Hand (FTT)

created by averaging subscale scores from the CPT-II, WMS-III Mental Control (MC), Trails B, and RFFT perseverative errors. The Working Memory (WM) composite was created by averaging the ACT and WAIS-III Arithmetic, Digit Span, and Letter-Number Sequencing subscale scores. The Processing Speed (PS) composite was created by averaging Trails A and WAIS-III Digit-Symbol Coding and Symbol Search subscale scores. The General Language (GL) composite was created by averaging WAIS-III Vocabulary, Similarities, and Information, COWAT, and BNT-2 subscale scores. The Visuospatial Processing (VSP) composite was created by averaging subscale scores from WAIS-III Picture Completion, Block Design, and Matrix Reasoning and RFFT unique designs and error ratio. The Motor Skills (MS) composite was created by averaging the Grooved Pegboard (GP) and Finger Tapping Test (FTT) subscale scores. This set of composite scores was developed based on a review of the literature of findings on combining neuropsychological findings into factors that are relevant to and appropriate for specific populations of study (i.e., schizophrenia; Thoma et al., 2003).

Performance on Measures of Verbal Memory

Bivariate correlations were performed between years of education, participant SES, and the overall VM composite. Both years of education (Pearson's $r = .357$, $p < .05$) and SES (Pearson's $r = -.416$, $p < .01$) were significantly correlated with VM. However, since the VM composite values were computed by averaging demographically-corrected standard scores, these variables had already been accounted for and thus were not covaried in subsequent analyses[1]. Thus, a one-way ANOVA, with VM value as the dependent variable and group membership as the independent variable, was performed to

[1] In follow-up analyses, education and SES were covaried with all outcome measures (VM, NVM, WM, PS, Language, Motor, VSP, and EA factors). The results did not differ from those reported here.

test the first hypothesis that the schizophrenia and left TLR groups would perform worse than the normal control group on VM. The overall test was significant [$F(3,39) = 5.00$, $p < .01$], indicating that there were group differences. Planned follow-up contrasts showed that, as predicted, both the schizophrenia group [$t(39) = 2.23$, $p < .05$] and the left TLR [$t(39) = 3.74$, $p < .01$] group had lower VM composite scores than the control group. Of note, a similar trend was noted for the right TLR group, with lower VM composite scores than the control group [$t(39) = 2.33$, $p < .05$]. The results of the VM analyses are presented in Table 5. Thus, the first hypothesis, that the schizophrenia and left TLR groups would perform worse than controls on measures of verbal memory, was confirmed.

Follow-up analyses were conducted on individual neuropsychological variables within the VM composite to determine whether there were significant differences between groups on specific measures. A multivariate analysis of variance (MANOVA) with individual verbal memory variables (see Table 4) as dependent variables and group membership as the independent variable was performed. The overall MANOVA was significant [Wilks's Lambda $F(48,72.176) = 2.06$, $p < .01$], indicating that there were group differences. Follow-up one-way ANOVAs revealed significant differences in LM1 [$F(3,29) = 3.37$, $p < .05$], LM% [$F(3,39) = 3.55$, $p < .01$], VPA1 [$F(3,39) = 5.87$, $p < ..001$], VPA2 [$F(3,39) = 6.32$, $p < .01$], CVLT1-5 [$F(3,39) = 2.99$, $p < .05$], SDFR [$F(3,39) = 3.30$, $p < .05$], and CVLTFP [$F(3,39) = 6.11$, $p < .01$]. Results approached significance for LM2 [$F(3,39) = 2.77$, $p = .054$] and LDCR [$F(3,39) = 2.56$, $p = .069$].

Planned follow-up contrasts were performed to determine the directionality of these results (see Figure 1). The schizophrenia group had significantly lower scores than

Table 5. Verbal Memory Outcomes by Group

	SCZ (n = 8)		LTLR (n = 13)		RTLR (n = 8)		NC (n = 14)	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
VM Composite*	-0.11[a]	0.86	-0.38[a]	0.67	-0.14[a]	0.52	0.50[b]	0.40
LM1**	-0.80[a]	1.13	-0.14	1.03	0.25	0.48	0.44[b]	0.88
LM2	-0.50	1.39	-0.36	0.97	0.23	0.37	0.48	0.82
LMrec	-0.53	1.45	-0.03	1.04	0.01	0.72	0.32	0.73
LM%**	-0.17[a]	1.22	-0.61[a]	0.94	0.06	0.87	0.63[b]	0.61
VPA1**	-0.13[a,c]	0.77	-0.84[a]	1.04	0.16[b,c]	0.35	0.76[b]	0.71
VPA2**	-0.20[a]	0.82	-0.73[a]	1.15	0.25	0.77	0.65[b]	0.51
VPArec	0.05	0.51	-0.43	1.74	0.24	0.00	0.24	0.00
VPA%	0.01	1.02	-0.42	1.27	0.01	0.87	0.38	0.66
CVLT1-5**	0.02	1.36	-0.29[a]	0.90	-0.54[a]	0.63	0.56[b]	0.81
ListB	-0.30	1.38	-0.16	1.06	-0.36	0.79	0.53	0.60
SDFR**	0.40	1.00	-0.50[a]	1.02	-0.38	0.99	0.49[b]	0.74
SDCR	0.01	0.94	-0.09	1.34	-0.45	0.83	0.34	0.68
LDFR	-0.03	1.34	-0.23	0.78	-0.46	1.21	0.50	0.69
LDCR	-0.07	1.13	-0.36	1.12	-0.32	0.96	0.56	0.60
CVLTHits	0.00	1.54	0.20	0.79	-0.59	1.08	0.15	0.69
CVLTFP**	0.24[a]	0.73	-0.83[b]	1.20	0.24[a]	0.43	0.50[a]	0.70

Note. SCZ = Schizophrenia group; LTLR = Left temporal lobe resection group; RTLR = Right temporal lobe resection group; NC = Normal control group; VM = Verbal Memory; see Table 4 for individual variable abbreviations. *ANOVA p <.01. Groups with different superscripts differ at the p <.05 level. **MANOVA p <.01. Groups with

Table 5 (cont.)

different superscripts differ at the $p < .05$ level (planned comparisons) or Bonferroni-corrected $p < .0125$ level (post-hoc comparisons).

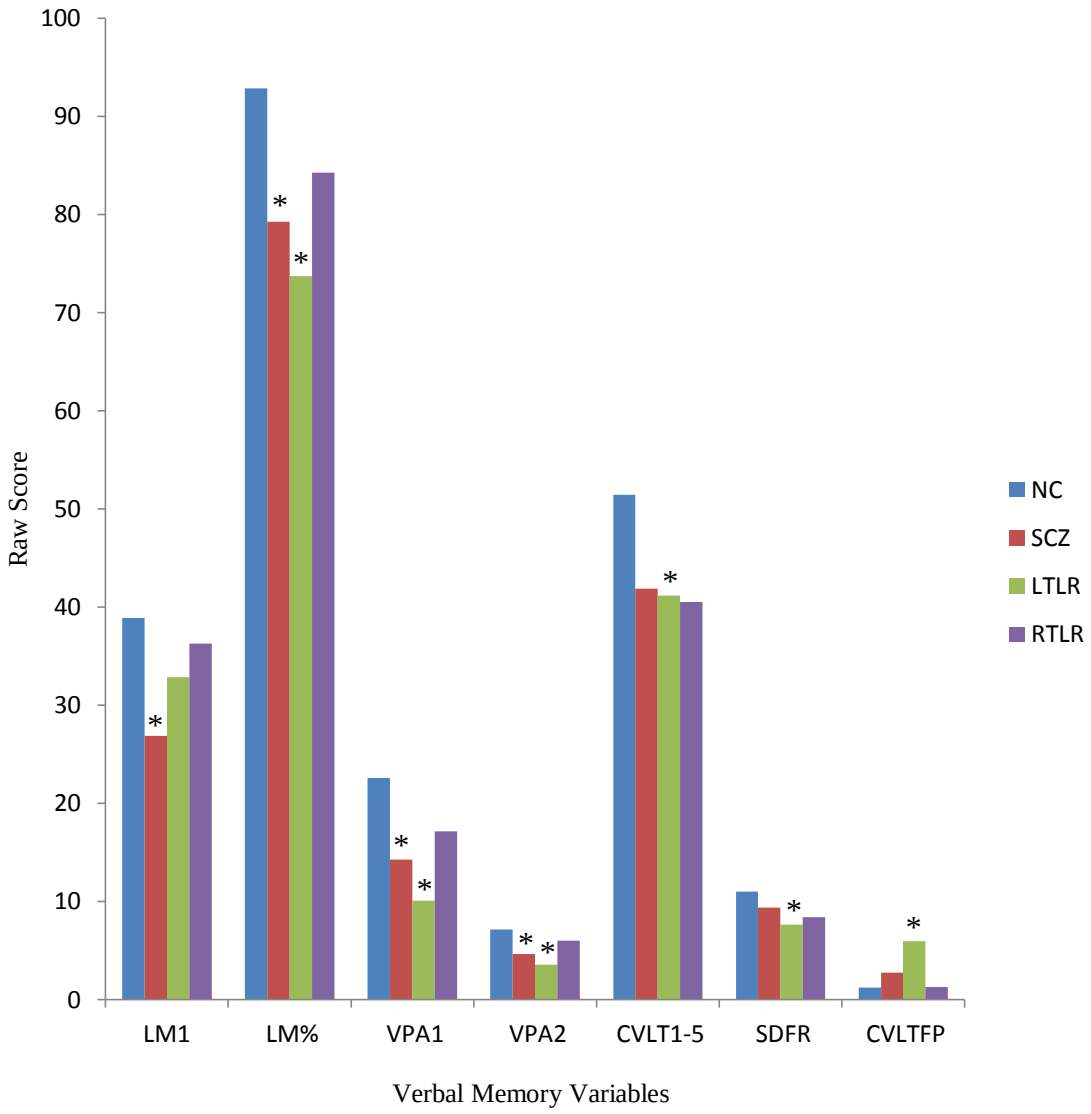

Figure 1 **Performance on Individual Measures of Verbal Memory by Group. NC = Normal control group; SCZ = Schizophrenia group; LTLR = Left temporal lobe resection group; RTLR = Right temporal lobe resection group; see Table 4 for individual variable names. *ANOVA p <.05; groups with an asterisk differ from NC at the p <.05 level.**

the control group on LM1 [$t(39) = 3.04$, $p < .01$], LM% [$t(39) = 2.02$, $p < .05$], VPA1 [$t(39) = 2.55$, $p < .05$], and VPA2 [$t(39) = 2.26$, $p < .05$]. The left TLR group had significantly lower scores than the control group on LM% [$t(39) = 3.58$, $p < .01$], VPA1 [$t(39) = 5.25$, $p < .001$], VPA2 [$t(39) = 4.22$, $p < .001$], CVLT1-5 [$t(39) = 2.37$, $p < .05$], SDFR [$t(39) = 2.64$, $p < .0125$], and CVLTFP [$t(39) = 4.03$, $p < .001$]. Thus, results from individual measures were generally consistent with the first hypothesis. The means and standard deviations of VM measures and results of the MANOVA and follow-up tests of VM are presented in Table 5.

Exploratory post-hoc contrasts using Bonferroni adjustments (i.e., $p < .0125$) were performed to determine whether significant differences on individual verbal memory measures were present among the other groups as well. Results showed that the left TLR group had significantly lower scores than the right TLR group on VPA1 [$t(39) = 2.82$, $p < .01$], and results approached significance in the same direction on VPA2 [$t(39) = 2.57$, $p = .014$]. For CVLT1-5, the right TLR group had significantly lower scores than the control group [$t(39) = 2.65$, $p < .0125$], and results approached significance between the left TLR and control groups [$t(39) = 2.37$, $p = .023$],with the left TLR group having lower scores. For CVLTFP, the left TLR group had significantly lower scores than the schizophrenia group [$t(39) = 2.80$, $p < .01$] and the right TLR group [$t(39) = 2.80$, $p < .01$]. The results of the post-hoc tests of VM are presented in Table 5.

Performance on Measures of Non-Verbal Memory

Bivariate correlations between education and the overall NVM composite were nonsignificant, however, SES and NVM were significantly correlated (Pearson's $r = -.348$, $p < .05$). As before, SES was not covaried in subsequent analyses since NVM was

calculated using demographically-corrected standard scores. Thus, a one-way ANOVA, with NVM value as the dependent variable and group membership as the independent variable, was performed to test the second hypothesis that the schizophrenia and right TLR groups would perform worse than the normal control group on NVM. Results of the overall ANOVA closely approached significance [$F(3,39) = 2.85$, $p = .05$]. Exploratory post-hoc contrasts showed that, as predicted, the right TLR group had significantly lower NVM composite scores than the control group [$t(39) = 2.87$, $p < .01$]. There was also a trend toward lower scores in the right TLR group than the left TLR group [$t(39) = 1.79$, $p = .08$], though results were not statistically significant. However, the schizophrenia group did not significantly differ from the control group. The results of the NVM analyses are presented in Table 6. Thus, the second hypothesis, that the schizophrenia and right TLR groups would perform worse than controls on measures of nonverbal memory, was only partially confirmed.

Since the overall ANOVA was very close to significance, exploratory post-hoc analyses were conducted on individual neuropsychological variables within the NVM composite to determine whether there were significant differences between groups on specific measures. A MANOVA with individual nonverbal memory variables (see Table 4) as dependent variables and group membership as the independent variable was performed. The results of the MANOVA are presented in Table 6. The overall MANOVA was not significant [Wilks's Lambda $F(21,95.3) = 1.35$, $p = .16$]. However, given that the overall ANOVA for NVM was so close to significance, exploratory one-way ANOVAs were performed on the individual NVM variables included in the MANOVA to determine whether performance differed between groups on either subtest

Table 6. Nonverbal Memory Outcomes by Group

	SCZ (n = 8)		LTLR (n = 13)		RTLR (n = 8)		NC (n = 14)	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
NVM Composite*	-0.12	0.92	0.02	0.55	-0.48[a]	0.71	0.32[b]	0.46
Faces1	-0.05	1.02	-0.20	1.00	-0.48	1.08	0.49	0.82
Faces2	-0.16	1.26	0.08	0.60	-0.28	1.58	0.18	0.77
Faces%	-0.03	1.06	0.38	0.80	0.13	1.29	-0.42	0.89
VR1**	-0.02	1.08	-0.29	1.04	-0.56[a]	0.86	0.60[b]	0.73
VR2**	-0.16	1.29	0.00	0.80	-0.71[a]	0.47	0.50[b]	1.01
VR-rec**	-0.13	1.31	-0.04	0.95	-0.99[a]	0.94	0.49[b]	0.77
VR%**	-0.31	1.51	0.17	0.78	-0.66[a]	0.46	0.39[b]	0.90

Note. SCZ = Schizophrenia group; LTLR = Left temporal lobe resection group; RTLR = Right temporal lobe resection group; NC = Normal control group; NVM = Nonverbal Memory; see Table 4 for individual variable abbreviations. *ANOVA p = .05. Groups with different superscripts differ at the p <.05 level. **Groups with different superscripts differ at the p <.05 level in planned follow-up contrasts.

(i.e., Faces or VR). Significant group differences were found for the VR subtest only: VR1 [F (3,39) = 3.34, p <.05], VR2 [F(3,39) = 2.92, p <.05], and VR-rec [F(3,39) = 3.96, p <.05]. Results approached significance for VR% [F(3,39) = 2.49, p = .07].

Planned contrasts were performed to determine the directionality of these differences (see Figure 2). The right TLR group had significantly lower scores than the control group on VR1 [t(39) = 2.82, p <.01], VR2 [t(39) = 2.90, p <.01], VR% [t(39) = 2.49, p <.05], and VR-rec [t(39) = 3.44, p <.01].

Exploratory post-hoc contrasts using Bonferroni adjustments (i.e., p <.0125) were performed to determine whether significant differences on individual non-verbal memory measures were present among the other groups as well. Results of all comparisons were non-significant.

Performance on Measures of Other Neuropsychological Domains

Several bivariate correlations between education, SES, and the overall neuropsychological factors (EA, MS, WM, PS, VSP, and GL) were significant (see Table 7). However, as before, education and SES were not covaried in subsequent analyses since all neuropsychological composite scores were calculated using demographically-corrected standard scores. Thus, a series of one-way ANOVAs, with composite value as the dependent variable and group membership as the independent variable, were performed to test the third hypothesis that the schizophrenia group would perform worse than the normal control group on measures of executive attention, motor skills, working memory, and processing speed. Overall ANOVAs were significant for motor skills [F(3,39) = 3.66, p <.05], general language [F(3,39) = 4.87, p <.01], working memory [F(3,39) = 3.37, p <.05], and processing speed [F(3,39) = 6.63, p <.01]. There were no

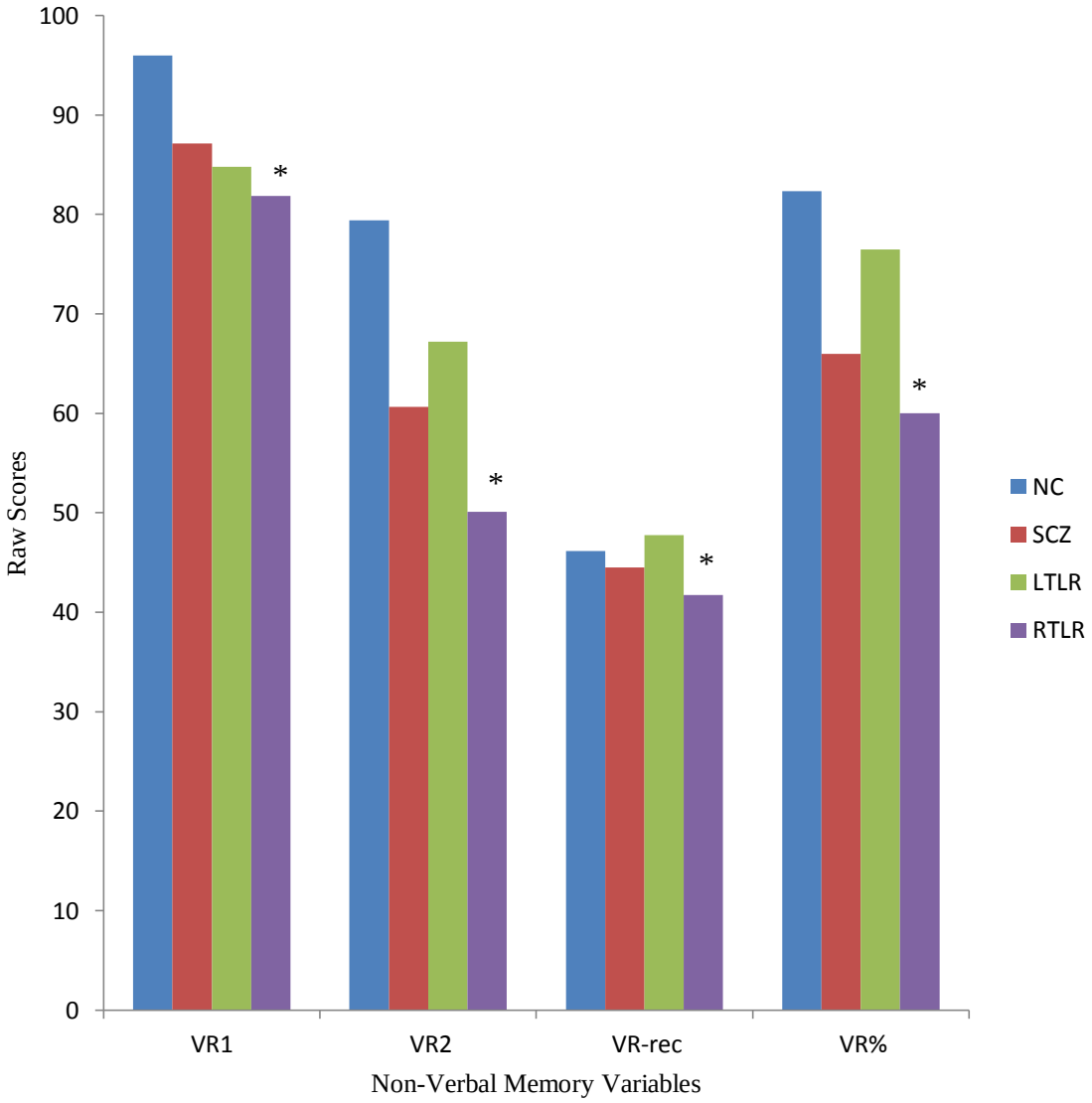

Figure 2 **Performance on Individual Measures of Non-Verbal Memory by Group. NC = Normal control group; SCZ = Schizophrenia group; LTLR = Left temporal lobe resection group; RTLR = Right temporal lobe resection group; see Table 4 for individual variable names. *ANOVA p =.05; groups with an asterisk differ from NC at the p <.05 level.**

Table 7. Pearson's Correlations Between Years of Education, Socioeconomic Status, and Neuropsychological Composite Scores

	Education	SES
Education		-.229
SES	-.229	
Executive Attention (EA)	-.070	-.005
Motor Skills (MS)	.464**	-.423*
Working Memory (WM)	.449**	-.565**
Processing Speed (PS)	.315*	-.450**
Visuospatial Processing (VSP)	.191	-.387*
General Language (GL)	.406**	-.452**

Note. SES = Socioeconomic Status (calculated using Hollingshead Index of Social Position). *Pearson's r <.05. ** Pearson's r <.01.

significant group differences on the executive attention or visuospatial factors. The results of these ANOVAs are presented in Table 8.

Planned follow-up contrasts were conducted to test the directionality of these results. As predicted, the schizophrenia group had lower scores than the control group on the motor skills composite [$t(38) = 2.19$, $p < .05$], the working memory composite [$t(39) = 2.46$, $p < .05$], and the processing speed composite [$t(39) = 4.16$, $p < .01$]. Thus, results confirm the third hypothesis for motor skills, working memory, and processing speed, though this hypothesis was not confirmed regarding executive attention skills.

Exploratory post-hoc contrasts using Bonferroni adjustments (i.e., $p < .0125$) were performed to determine whether significant differences on neuropsychological factors were present among the other groups as well. Results showed that the left TLR group had lower scores than the control group on the motor skills composite [$t(38) = 3.18$, $p < .01$] and the general language composite [$t(39) = 3.67$, $p < .01$]. The right TLR group had significantly lower scores than the control group on the working memory composite [$t(39) = 2.74$, $p < .01$] and the processing speed composite [$t(39) = 2.98$, $p < .01$]. The results of the post-hoc tests of other neuropsychological factors are presented in Table 8.

Memory Profile Patterns

To test the fourth hypothesis, that the memory profile of the schizophrenia group would more closely resemble that of the left TLR group than the right TLR group, a mixed-model (repeated measures) ANOVA with diagnosis as the group factor and memory composite (immediate and delayed verbal and non-verbal memory; see Table 9 for composite labels and individual variables included in each composite) as the factor variable was conducted. Results showed a significant a significant main effect for Group

Table 8. Non-Memory Neuropsychological Composite Outcomes by Group

	SCZ (n = 8)		LTLE (n = 13)		RTLE (n = 8)		NC (n = 14)	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
EA	-0.14	0.44	-0.01	0.88	0.26	0.42	0.12	0.54
MS*	-0.17[a]	1.04	-0.35[a]	0.66	-0.05	0.61	0.49[b]	0.40
WM*	-0.37[a]	0.71	-0.10	0.96	-0.46[a]	0.75	0.45[b]	0.53
PS**	-0.67[a]	0.52	-0.04	0.81	-0.31[a]	0.62	0.59[b]	0.67
VSP	-0.10	0.51	-0.02	0.76	-0.41	0.40	0.23	0.55
GL**	0.18	0.71	-0.49[a]	0.56	-0.18	0.79	0.46[b]	0.68

Note. SCZ = Schizophrenia group; LTLR = Left temporal lobe resection group; RTLR = Right temporal lobe resection group; NC = Normal control group; EA = Executive Attention composite; MS = Motor Speed composite; WM = Working Memory composite; PS = Processing Speed composite; VSP = Visuospatial Processing composite; GL = General Language composite. *ANOVA p <.05. **ANOVA p <.01. Groups with different superscripts differ at the p <.05 level (planned comparisons) or Bonferroni-corrected p <.0125 level (post-hoc comparisons).

Table 9. Individual Variables within Immediate and Delayed Verbal and Nonverbal Memory Composite Factors and Their Abbreviations

Composite Factor	Measures Included	Individual Variables Included
Immediate Verbal Memory (IVM)	WMS-III	Logical Memory I (LM1); Verbal Paired Associates I (VPA1)
	CVLT-II:	Trials 1-5 Total (CVLT1-5); List B Total (ListB); Short-Delay Free Recall (SDFR); Short-Delay Cued Recall (SDCR)
Delayed Verbal Memory (DVM)	WMS-III: LM	Delayed Recall (LM2); Recognition (LM-rec); Percent Retention (LM%)
	WMS-III: VPA	Delayed Recall (VPA2); Recognition (VPA-rec); Percent Retention (VPA%)
	CVLT-II:	Long-Delay Free Recall (LDFR); Long-Delay Cued Recall (LDCR); Recognition Hits (CVLT-Hits); Recognition False Positives (CVLTFP)
Immediate Non-Verbal Memory (INVM)	WMS-III:	Faces I (Faces1); Visual Reproduction I (VR1)
Delayed Non-Verbal Memory (DNVM)	WMS-III: Faces	Delayed Recognition (Faces2); Percent Retention (Faces%)
	WMS-III: VR	Delayed Recall (VR2); Recognition (VR-rec); Percent Retention (VR%)

[$F(3,39) = 4.56$, $p < .01$]. Planned follow-up contrasts using Fisher's Least Significant Difference corrections showed that the schizophrenia [$p < .05$], left TLR [$p < .01$], and right TLR [$p < .01$] groups were all significantly different from the control group, but were not significantly different from each other. However, the main effect must be interpreted in the context of a significant Group x Factor interaction [$F(3,39) = 3.14$, $p < .05$]. Figure 3 depicts the complexity of the interactions present in the analyses.

In order to delineate the pattern of differences in this complex interaction, we first wished to test the consistency of our TLR data with that of previously reported results in the literature. To do so, a repeated-measures ANOVA with diagnosis (left and right TLR) as the group factor and memory composite (immediate and delayed verbal and non-verbal memory) as the factor variable was conducted. There was no main effect for group ($p = .66$), but the Group x Factor interaction was significant [$F(1,19) = 5.08$, $p < .05$], with the left TLR group scoring more poorly on verbal memory factors and the right TLR group scoring more poorly on non-verbal memory factors (see Figure 4, which is a simplified version of Figure 3). These results are consistent with the existing literature on memory patterns in TLR, thus a second repeated-measures ANOVA with the schizophrenia group included in the group factor was conducted to investigate the effect of this data on the interaction. With the addition of the schizophrenia group, the main effect was not significant [$F(2,26) = .241$, $p = .79$], and the interaction approached significance [$F(4.22,54.82) = 2.30$, $p = .07$]. However, post-hoc within-subjects contrasts showed no significant main effects or interaction effects between levels of the memory factor (see Figure 5, again a simplified version of Figure 3). Thus, the fourth hypothesis, that the

memory profile of the schizophrenia group would more closely resemble that of the left TLR group than the right TLR group, was not supported.

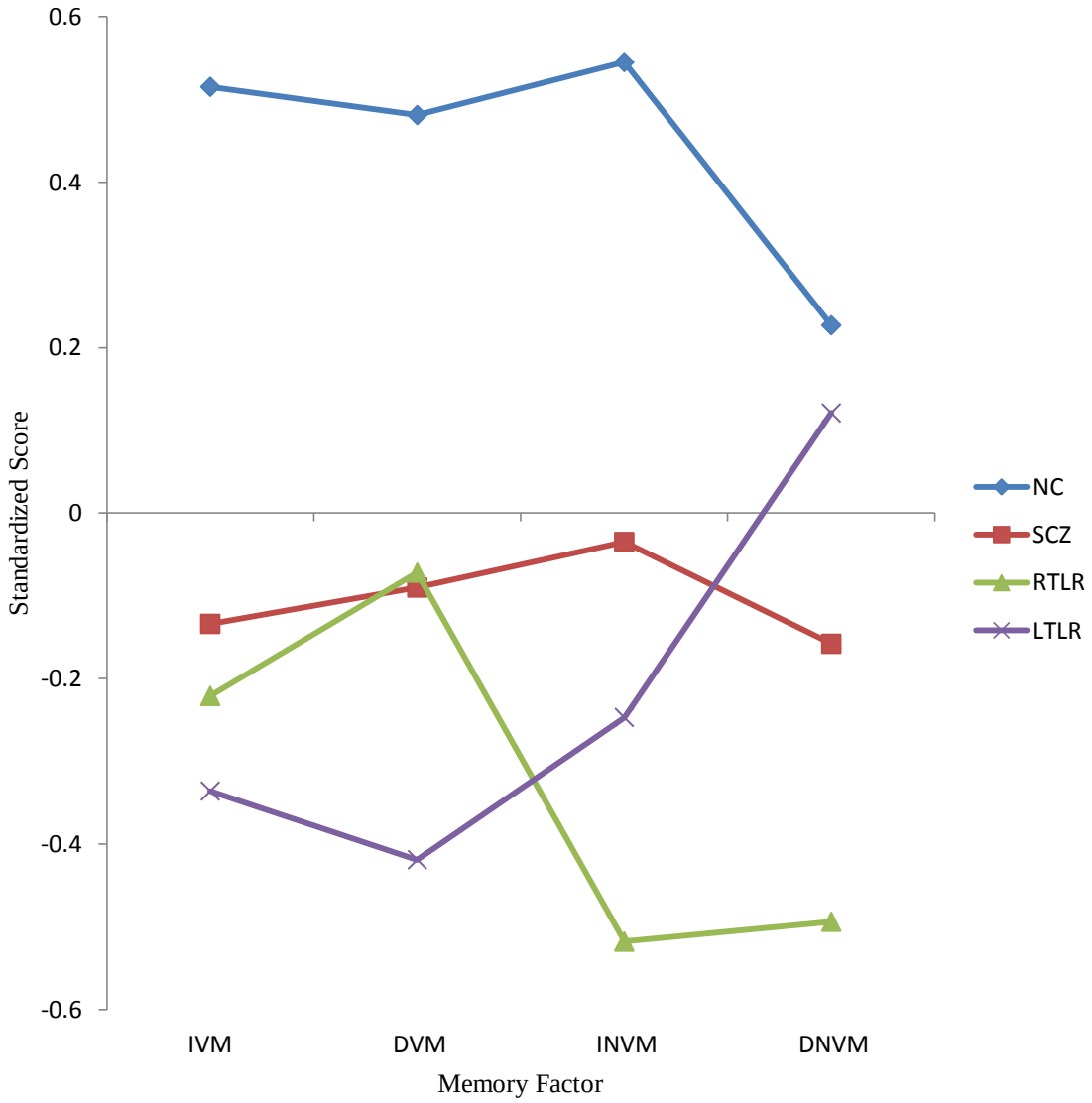

Figure 3 **Memory Profiles by Group. NC = Normal control group; SCZ = Schizophrenia group; LTLR = Left temporal lobe resection group; RTLR = Right temporal lobe resection group; IVM = Immediate Verbal Memory composite; DVM = Delayed Verbal Memory composite; INVM = Immediate Non-Verbal Memory composite; DNVM = Delayed Non-Verbal Memory composite.**

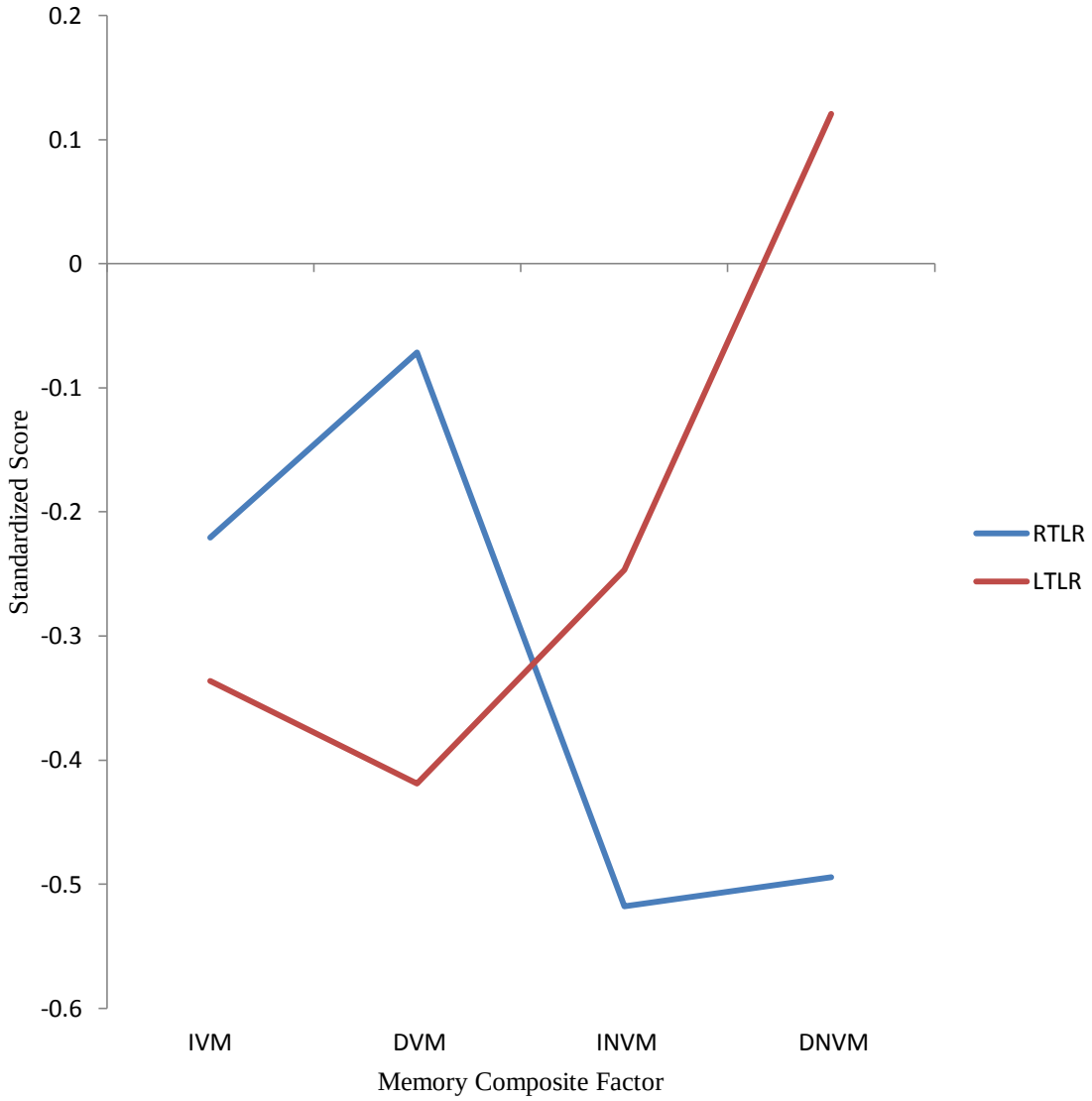

Figure 4 **Performance on Memory Composites by Group. LTLR = Left temporal lobe resection group; RTLR = Right temporal lobe resection group; IVM = Immediate Verbal Memory composite; DVM = Delayed Verbal Memory composite; INVM = Immediate Non-Verbal Memory composite; DNVM = Delayed Non-Verbal Memory composite.**

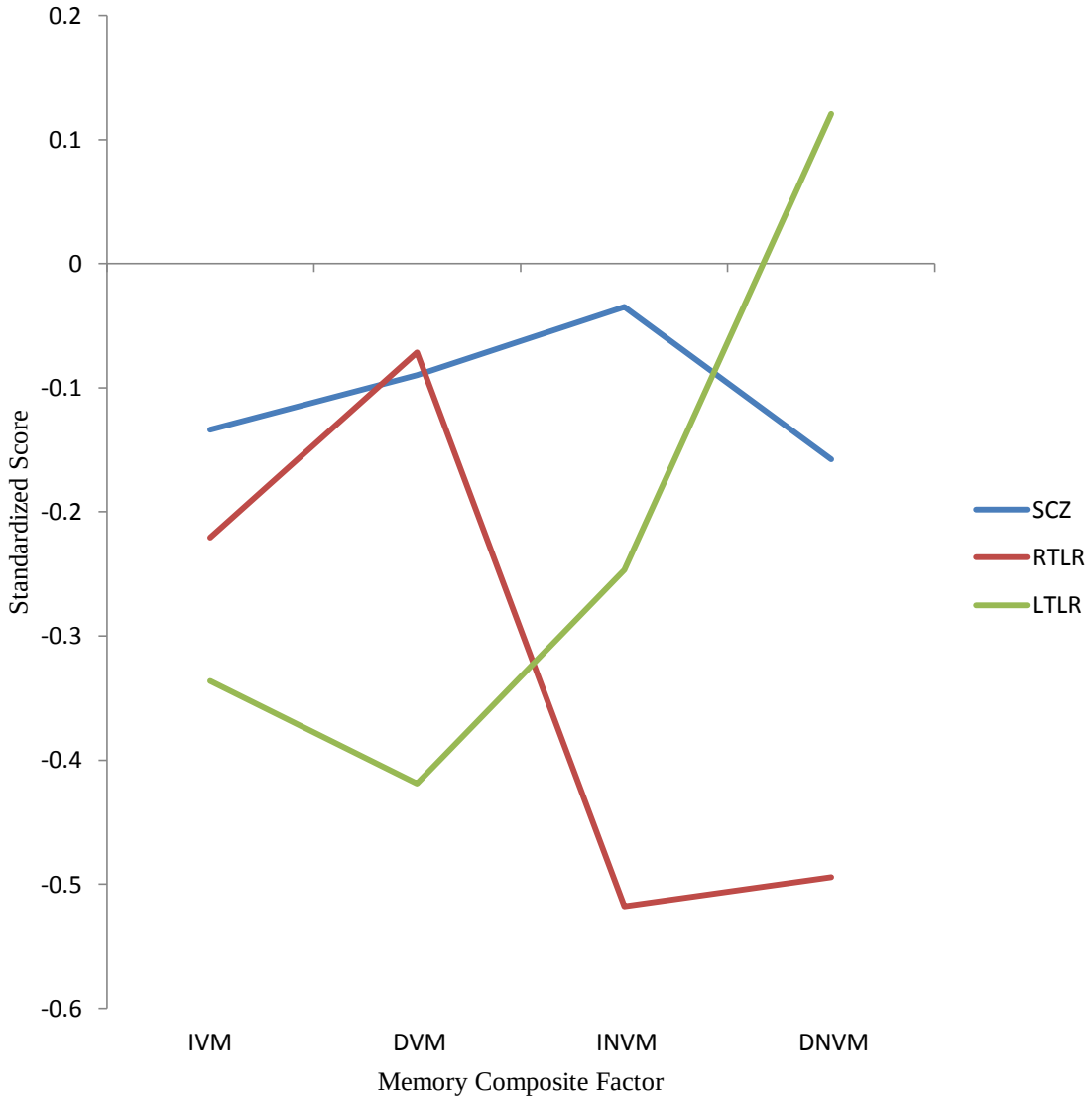

Figure 5 **Performance on Memory Composites by Group. SCZ = Schizophrenia group; LTLR = Left temporal lobe resection group; RTLR = Right temporal lobe resection group; IVM = Immediate Verbal Memory composite; DVM = Delayed Verbal Memory composite; INVM = Immediate Non-Verbal Memory composite; DNVM = Delayed Non-Verbal Memory composite.**

Post-hoc Exploratory Analyses of Neuropsychological Factors

To extend the scope of hypothesis four and investigate whether specific neuropsychological performance profiles across multiple domains may better characterize any pattern similarities between the schizophrenia and TLR groups, an exploratory discriminant function analysis utilizing the entire set of neuropsychological variables available was conducted to determine whether the eight factors (verbal memory, non-verbal memory, motor skills, general language, visuospatial processing, working memory, processing speed, and executive attention) could predict group membership. The overall Wilks's lambda was significant, [$\Lambda = .25$, $\chi^2(24, N = 43) = 49.15$, $p < .01$], indicating that overall the predictors differentiated among the four diagnostic groups. In addition, the residual Wilks's lambda was significant, [$\Lambda = .48$, $\chi^2(14, N = 43) = 25.34$, $p < .05$]. This test indicated that the neuropsychological factors differentiated significantly among the four diagnostic groups after partialling out the effects of the first discriminant function. Because these tests were significant, both discriminant functions were interpreted.

In Table 10, the within-groups correlations between the predictors (i.e., neuropsychological composite factors) and both discriminant functions, as well as the standardized weights, are presented. Based on these coefficients, the Processing Speed composite demonstrates the strongest relationship with the first discriminant function, with Working Memory and Nonverbal Memory showing slightly weaker, but still significant, relationships. The General Language factor demonstrated the strongest relationship with the second discriminant function, with Verbal Memory and Motor Skills showing weaker yet significant relationships. On the basis of the results presented in

Table 10. Standardized Coefficients and Correlations of Neuropsychological Predictor Variables with the Two Discriminant Functions

Predictor Variable	Correlation coefficients with discriminant functions		Standardized coefficients for discriminant functions	
	Function 1	Function 2	Function 1	Function 2
Processing Speed	.748*	.064	1.099	-.175
Working Memory	.525*	.075	.335	-.707
Non-Verbal Memory	.457*	-.006	.117	-.579
General Language	.297	.597*	-.029	.805
Verbal Memory	.450	.507*	.210	.712
Motor Skills	.385	.428*	-.348	.530
Executive Attention	.005	.053	-.669	-.143
Visuospatial Processing	.398	.022	.000	.009

Note. *Variable is a significant predictor within the function specified.

Table 10, we labeled the first discriminant function Attention-NVM and the second discriminant function Language-VM.

Although the outcomes of the discriminant function analysis do not indicate which groups are being discriminated by the functions, the means on the discriminant functions are consistent with the interpretation of the first function as loading heavily on attentional processing and nonverbal memory, and with the interpretation of the second function as loading heavily on language skills, including verbal memory. The normal control group had the highest mean on the Attention-NVM function (M = 1.24) and the left TLR group had the next highest mean (M = .022), while the schizophrenia (M = -1.02) and right TLR group (M = -1.03) had the lowest mean scores. On the other hand, the schizophrenia (M = .600) and normal control (M = .569) groups had the highest mean scores on the Language-VM function, followed closely by the right TLR group (M = .475), while the left TLR group had the lowest mean score (M = -1.23).

Utilizing the discriminant function analysis to predict diagnostic group membership (i.e., control, schizophrenia, left TLR, or right TLR), 73.8% of the individuals in our sample were able to be correctly classified. In order to take into account chance agreement, a kappa coefficient was computed; the value of kappa was .645, indicating moderate to high accuracy in prediction. Finally, to assess how well the classification procedure would predict in a different sample, the leave-one-out technique was applied. The percent of individuals correctly classified based on this technique was estimated at 45.2%.

Discussion

Summary

Previous research has been suggestive of significant left-hemisphere frontotemporal dysconnectivity and resulting dysfunction in schizophrenia (e.g., Baaré et al., 1999; Bogerts et al., 1990; Breier et al., 1992; Bryant et al., 1999; Buchanan, Vladar, Barta, & Pearlson, 1998; DeLisi et al., 1991; Gur et al., 1998; Hirayasu et al., 1998; Hoff et al., 1999; Honea et al., 2005; Pearlson, Petty, Ross, & Tien, 1996; Shenton et al., 1992, 2001; Turetsky et al., 1995; Velakoulis et al., 2006; Weinberger, Berman, Suddath, & Torrey, 1992; Wible et al., 1995). In particular, hippocampal dysfunction has been implicated as a core feature of schizophrenia resulting in impaired verbal, and to a lesser extent, visual memory (Harrison, 2004; Thoma et al., 2008). In the current study, it was hypothesized that, overall, participants with schizophrenia would demonstrate a pattern of performance on multiple memory tests similar to that of individuals who had undergone temporal lobe, including hippocampus, resection for intractable epilepsy. Specifically, given the significant evidence in the literature for left-hemisphere temporal lobe involvement in schizophrenia, it was reasonable to hypothesize that while multiple neuropsychological domains may be affected in schizophrenia, verbal memory deficits may be especially apparent and similar to those reliably described in individuals with temporal lobe epilepsy localized to the left hemisphere (e.g., Aleman, Hijman, de Haan, & Kahn, 1999; Clare, McKenna, Mortimer, & Baddeley, 1993; Delaney, Rosen, Mattson, & Novelly, 1980; Giovagnoli, Casazza, & Avanzini, 1995; Hanlon et al., 2006; Hoff et al., 1999; Johnson, Klinger, & Williams, 1977; Ladavas, Umilta, & Provincialo, 1979; Majdan, Sziklas, & Jones-Gotman, 1996; Nacmani & Cohen, 1969; Ojemann & Dodrill,

1985; Toulopoulou, Morris, Rabe-Hesketh, & Murray, 2003). Namely, in addition to impairments in attention (e.g., working memory and processing speed), executive functioning, and motor skills, individuals with schizophrenia were expected to demonstrate impaired verbal memory, similar to a left temporal lobe resection (TLR) group, and impaired nonverbal memory, similar to a right TLR group, with an overall memory profile more similar to the left TLR group, highlighting the importance of left-hemispheric temporal lobe dysfunction in schizophrenia.

Verbal Memory

The first hypothesis, that the schizophrenia and left TLR groups would both perform more poorly on verbal memory tasks than a healthy control group, was supported. The schizophrenia group performed worse than controls on measures of contextual verbal memory (WMS-III Logical Memory) and paired-associative verbal learning (WMS-III Verbal Paired Associates), and the left TLR group performed worse than controls on measures of contextual verbal memory, paired-associative verbal learning, and rote verbal learning and recall (CVLT-II). Of note, there were no clinically significant differences between the schizophrenia group and the left TLR group on any of these variables, suggesting that the verbal memory performance of individuals with schizophrenia in this sample was similar to that of those individuals who had undergone left TLR. Consistent with previous research (e.g., Aleman, Hijman, de Haan, & Kahn, 1999; Clare, McKenna, Mortimer, & Baddeley, 1993; Hanlon et al., 2006), immediate and delayed recall for verbal information appears to have been more affected than recognition memory, as the only significant difference on recognition variables which emerged was a higher number of false positive errors on the CVLT-II committed by the

left TLR group compared to controls. That is, the number of correctly recognized items on this test was not significantly different across groups. This pattern is consistent with previous theories which suggest that the difficulties with verbal memory seen in schizophrenia may be the result of poor encoding and retrieval of information rather than deficient storage of material (e.g., Aleman, Hijman, de Haan, & Kahn, 1999; Heaton, Miller, Taylor, & Grant, 1994; McClain, 1983; Paulsen et al., 1995).

The pattern of performance in the left TLR group is also consistent with previous research which has demonstrated significant impairment in recall of verbal information in left TLE/TLR patients (e.g., Delaney, Rosen, Mattson, & Novelly, 1980; Ladavas, Umilta, & Provinciali, 1979; Majdan, Sziklas, & Jones-Gotman, 1996; Ojemann & Dodrill, 1985). Prior studies have demonstrated that verbal learning on the CVLT-II (i.e., total items recalled on trials 1-5) is highly correlated with hippocampal neuropathology and is a strong indicator of seizure lateralization in patients with TLE, with the strongest association emerging between verbal learning and left hippocampal neuron loss (Baños et al., 2004; Sass et al., 1995). Interestingly, in the current study, the left TLR group, but not the schizophrenia group, demonstrated poorer performance than controls on rote verbal learning and recall. It is possible that the extent of temporal lobe injury and resection in the TLR group limits the ability to learn and recall verbal information regardless of type of presentation, versus a structurally intact yet functionally impaired temporal lobe in schizophrenia which impacts complex verbal learning and memory requiring more developed general language skills. However, previous research has demonstrated impairments in learning, retrieval, and to a lesser extent, recognition, on the CVLT-II in a wide variety of patients with schizophrenia (e.g, Altshuler et al., 2004; Hill, Beers,

Kmiec, Keshavan, & Sweeny, 2004; Paulsen et al., 1995), typically in the context of a generalized neurocognitive deficit including impaired attention and executive functioning. The schizophrenia group in the current study did not demonstrate generalized neuropsychological impairment, which may explain why there were no differences in their rote verbal learning compared to controls. Regardless, the similar patterns of verbal memory performance overall in the left TLR group and the schizophrenia group provide some empirical support for the hypothesis that left-hemisphere temporal lobe dysfunction may be a core feature of schizophrenia.

Non-Verbal Memory

The second hypothesis was that the schizophrenia and right TLR groups would perform more poorly than the healthy control group on measures of non-verbal memory. Although this hypothesis was not confirmed, the results were in the predicted direction and very closely approached significance for the right TLR, but not for the schizophrenia, group. The right TLR group performed worse than controls on all aspects of the WMS-III Visual Reproduction subtest (i.e., immediate and delayed free recall, retention, and recognition); however, the results of the schizophrenia group were not significantly different from those of the control group on any measure of nonverbal memory. The current results are consistent with previous research demonstrating a visual memory deficit in patients with right-hemisphere TLE/TLR (e.g., Delaney, Rosen, Mattson, & Novelly, 1980; Giovagnoli, Casazza, & Avanzini, 1995; Gleiβner, Helmstaedter, & Elger, 1998; Ladavas, Umilta, & Povinciali, 1979). In contrast, prior studies of visual memory in schizophrenia have been somewhat inconsistent, with some demonstrating impairments (e.g., Calev, Korin, Kugelmass, & Lerer, 1987; Gold et al., 1992b; Kolb &

Whishaw, 1983; Rushe, Woodruff, Murray, & Morris, 1999; Sullivan, Shear, Zipursky, Sagar, & Pfefferbaum, 1994) and others showing relatively minor impairment compared to verbal memory impairment or an impairment only in nonverbal encoding (e.g., Saykin et al., 1991; Tracy et al., 2001). A complete lack of nonverbal memory impairment in patients with schizophrenia in the current study is surprising, however, given the overall cognitive profile in which statistically, but not necessarily clinically, significant differences between performance on neuropsychological measures in this group compared to controls suggests that the schizophrenia group in the current study may be particularly high-functioning. Thus, the results must be interpreted with some caution, as they are in contradiction to the results of the predominance of previous studies. On the other hand, in conjunction with previous research which demonstrates significant left-hemisphere neuroanatomical and neurocognitive abnormalities (e.g., Gur et al., 1998; Shenton et al., 1992; Siedman et al., 2002; Turetsky et al., 1995), the results of the current study suggest that left temporal and fronto-temporal dysfunction may be more prominent than bilateral temporal or fronto-temporal dysfunction in schizophrenia and lend support to the left-hemisphere theory of schizophrenia.

Other Neuropsychological Domains

The third hypothesis, that the schizophrenia group would perform more poorly than controls on measures of executive function/attention, motor skills, working memory, and processing speed, was partially confirmed. Consistent with previous research (Braff & Saccuzzo, 1985; Buchanan, Summerfelt, Tek, & Gold, 2002; Carter et al., 1998; Egeland et al., 2003; Goldman-Rakic, 1994; Heinrichs & Zakzanis, 1998), results showed that the schizophrenia group had lower composite scores than the control group on

indices of working memory, motor skills, and processing speed. The executive attention factor in the current study was comprised of measures which assess mental set-shifting (i.e., WMS-III Mental Control and Trail Making Test, Part B), perseveration/cognitive inflexibility (RFFT perseverative errors), and sustained visual attention (CPT-2). It is somewhat surprising that the schizophrenia group did not demonstrate impaired performance on the executive attention composite, as executive functioning impairment has been fairly reliably demonstrated in previous studies (e.g., Bilder et al., 2000; Braff et al., 1991; Goldberg & Gold, 1995; Hutton et al., 1998; Martínez-Arán et al., 2002; Velligan & Bow-Thomas, 1999). There are several possibilities which may explain the lack of a significant difference between patients with schizophrenia and healthy controls in the current study. First, many previous studies included the Wisconsin Card Sorting Test (WCST) in their protocols; this is a widely used neuropsychological measure of executive function which also requires intact working memory and visual attention. It is possible that had this measure been included in the present study, it may have captured an executive function deficit if indeed one was present. Patients with schizophrenia have fairly consistently demonstrated impaired performances on the WCST (Heinrichs & Zakzanis, 1998), though research relating to correlation of WCST results with positive and negative symptoms of schizophrenia have been less consistent (e.g., Braff et al., 1991; McGrath et al., 1997; Morice, 1990; Nieuwenstein, Aleman, & de Haan, 2001; Seidman et al., 1991). As schizophrenia subtype and positive/negative symptomatology were not evaluated in the present study, including the WCST in the current protocol may not have altered the results regarding executive attention.

A second possibility is that by analyzing only the composite score for executive attention, differences on individual variables within this composite may have been overlooked. To explore this possibility, post-hoc analyses were conducted on the individual variables within the executive attention factor: significant differences were found only for WMS-III Mental Control (schizophrenia and right TLR groups worse than controls) and CPT-2 commission errors (right TLR group worse than control and schizophrenia groups). Thus it seems that the schizophrenia group in the present study performed more poorly than healthy controls only on a measure of mental set-shifting. These results are consistent with the possibility that the patients with schizophrenia in this study may represent a relatively high-cognitive-functioning group, as suggested by their overall standardized scores within one standard deviation of average, indicating a lack of a generalized neurocognitive deficit. In general, however, current results are in keeping with those of previous studies regarding poor performance on measures of working memory, processing speed, and motor skills.

Overall Memory and Neuropsychological Profiles

The final hypothesis was that, overall, the memory pattern of the schizophrenia group would more closely resemble that of the left than the right TLR group. This hypothesis was not supported, as the schizophrenia group's scores on composites of immediate and delayed verbal and non-verbal memory were intermediate between those of the left and right TLR groups, and were not significantly different from either TLR group. That is, while the left and right TLR groups demonstrated the predicted interactive pattern of poorer verbal memory (left TLR) versus poorer non-verbal memory (right TLR), the schizophrenia group demonstrated a relatively flat pattern in which neither

verbal nor non-verbal memory scores were significantly different from each other. In fact, plotting the memory composite scores for the schizophrenia group resulted in a profile which most closely resembled that of the control group, although the scores were significantly lower than those of the control group.

The results of the exploratory discriminant function analysis which utilized all neuropsychological factors are intriguing. Two functions emerged which significantly predicted group membership: Attention-NVM and Language-VM. Regarding the Attention-NVM function, attentional skills, including working memory, processing speed, and sustained visual and auditory attention are known to be impaired in schizophrenia (Goldstein, Rosenbaum, & Taylor, 1997; Nieuwenstein, Aleman, & de Haan, 2001; Nuechterlein et al., 1994), thus the importance of this factor in discriminating between schizophrenia and control groups is quite obvious. Its role in differentiating between schizophrenia and TLR groups is less clear. Previous research has demonstrated that within left-hemisphere TLE/TLR groups, verbal memory is impaired while simple and sustained auditory attention are relatively spared (Fleck et al., 1999; Fleck, Shear, & Strakowski, 2002; Gold et al., 1994; Mirsky, Primac, Marsan, Rosvold, & Stevens, 1960). This may suggest that the functional neuroanatomy which is characteristic of left TLE (i.e., medial and lateral temporal lobe structural abnormalities) is closely associated with a specific verbal memory impairment, while in schizophrenia, impaired verbal and non-verbal memory coincide with impaired attentional functions, providing support for the involvement of the frontal lobe and its connections as well as temporal lobe dysfunction. Prior research has implicated abnormalities in fronto-temporal networks and the cognitive functions subserved by these connections (e.g., executive

function, attentional processing) as key features of schizophrenia (Green, 1998; Randolph, Goldberg, & Weinberger, 1993), and the results of the current study are generally consistent with this theory: the normal control and left TLR groups, in which no attentional or non-verbal memory deficits would be expected, had the highest means on the Attention-NVM factor, while the schizophrenia group, in which attentional and non-verbal memory impairment would be expected, as well as the right TLR group with expected non-verbal memory impairment, demonstrated the lowest means. The results of this discriminant function highlight the importance of assessing attention as a precursor to memory impairment in schizophrenia, and lend support to the existing literature describing impairments in fronto-temporal systems in this population.

On the second discriminant function, general language processing skills (such as expressive vocabulary, verbal abstract reasoning, and verbal fluency) and verbal memory, as well as motor skills, emerged as significant predictors of group membership. Interestingly, this function seemed to discriminate only the left TLR group from the other groups, as the control, schizophrenia, and right TLR groups all had relatively high means on this function whereas the left TLR group had a much lower mean score. While the contribution of language and verbal memory as discriminating between the left TLR group versus healthy controls and the right TLR group is consistent with previous research demonstrating deficits in these domains within left TLE/TLR groups (e.g., Hermann, Seidenberg, Haltiner, & Wyler, 1992; Ojeman & Dodrill, 1885; Richardson et al., 2004), it is somewhat surprising that the schizophrenia group in the current study displayed such a high mean on this function, given their overall lower performance on verbal memory measures compared to controls. It is possible that language and verbal

memory develop along different trajectories in schizophrenia versus in TLE, so that relatively poorer overall language development in TLE in conjunction with difficulties in verbal memory present as a more significant overall deficit than generally intact overall language processing skills combined with impaired verbal memory in schizophrenia. In a study by Gold and colleagues (1994), results showed that patients with schizophrenia performed better than patients with TLE on a measure of sight reading thought to predict premorbid potential, and demonstrated better semantic knowledge than patients with left-hemisphere TLE. The authors concluded that schizophrenia and TLE follow different developmental pathways, with TLE affecting the acquisition of academic skills such as vocabulary and semantic knowledge as well as cognitive functions, while in schizophrenia, language development is relatively spared, though cognitive functions such as verbal memory are significantly affected. The results of the Language-VM discriminant function in the current study are consistent with this theory, as the group means would seem to indicate that the schizophrenia group could be distinguished from the left TLR group on the basis of performance on measures of general language processing, given that these two groups performed similarly on measures of verbal memory.

Overall Conclusions

This is one of few studies to directly compare verbal and non-verbal memory functions, as well as other neuropsychological domains, in schizophrenia and temporal lobe epilepsy groups. As such, complex neuropsychological profiles which could demonstrate similarities and differences between these groups were able to be constructed, in order to further clarify the memory deficits typically reported in the

schizophrenia literature and determine whether the results were consistent with the theory that the symptoms and cognitive impairment associated with schizophrenia are largely the result of left-hemispheric dysfunction. In addition, the battery of tests administered in the current study included measures of multiple neuropsychological domains, which allowed an examination of a general versus domain-specific deficit in order to supplement the existing literature. The results of this study, which included significantly worse performances in verbal memory, processing speed, working memory, and motor skills, are consistent with previous research which has demonstrated several domain-specific impairments, (Bilder, 1996; Bilder et al., 2000; Braff et al., 1991; Goldberg & Gold, 1995; Pantelis, Nelson, & Barnes, 1996; Saykin et al., 1994); however, although significant differences were observed, the schizophrenia group's overall performance on all measures remained within the average to low average range, which would not be expected if a generalized neurocognitive deficit were present. In addition, the results of a discriminant function analysis did not yield a single factor which accounted for a substantial amount of variance within the schizophrenia group, further supporting the theory that several domain-specific deficits (or, in our sample, significantly worse performances) are present within a neurocognitive profile in schizophrenia.

Though comparisons of memory profiles between patients with schizophrenia and those who had undergone left- or right-TLR did not show the predicted pattern, the results of a discriminant function analysis do provide support for the presence of fronto-temporal dysfunction which may be mediated by cognitive functions such as language processing that functionally dissociate to the left hemisphere. Given the proximity of language processing areas to structures of the left temporal lobe associated with memory

(i.e., hippocampus), the results of the current study, which implicate abnormal hippocampal function (verbal memory) in the absence of impaired language functioning in the schizophrenia group, but not in the left TLR group, would seem to warrant further exploration of the hypothesis that structural and functional abnormalities in the hippocampus may be a core feature of schizophrenia, which have downstream effects on frontal and prefrontal lobe functioning. For example, previous research with rats has demonstrated that hippocampal insult results in prefrontal changes: neonatal damage to the ventral hippocampus alters the response of medial prefrontal cortical pyramidal neurons to dopaminergic/GABA-ergic projections from the midbrain, an effect which has been postulated to explain the impact of damage to human hippocampus in schizophrenia (O'Donnell, Lewis, Weinberger, & Lipska, 2002). Lipska (2004) described a series of studies which suggest that neonatal excitotoxic disconnection of the ventral hippocampus in rats result in a model of neurobiological and behavioral sequelae similar to those seen in humans with schizophrenia, including deficits in social functioning and working memory and changes in the development of frontal and prefrontal cortical regions. Further investigation of the hippocampus as a site of primary deficit in schizophrenia may help delineate the complex frontal-temporal disconnects seen in neuroimaging and neuropsychological studies.

Additional factors may also have contributed to the results of this study regarding demonstration of group differences. First, test characteristics such as familiarity of items (e.g., word lists versus abstract geometric figures) and type of stimulus presentation (e.g., free recall of word lists versus recognition of faces) may vary in their relative cognitive demands. Recall for stimulus items to which participants have had exposure prior to

testing (such as words from the CVLT-II) may result in differential neuronal activation patterns than recall for non-familiar stimulus items (such as the abstract designs from WMS-III VR), such that additional neuronal networks are involved in the encoding and retrieval of these items. Likewise, verbal material may be more easily 'chunked' in learning trials and related to an individual's personal experience with language (e.g., utilizing mnemonic strategies to learn rote verbal material), whereas no previous template or learning strategy may exist for abstract visual material.

A second factor which may have affected the results of this study in terms of group differences is the purported laterality of the TLR groups. Neuronal processes such as extent of regenesis, dendritic branching, and contralateral compensation (i.e., the non-affected hemisphere assuming some of the functions of the affected hemisphere) following cerebral insult may all play a role in the cognitive functioning of post-surgical patients as well as in patients with schizophrenia. However, the TLR patients in the current study all underwent intracarotid sodium amobarbital (Wada) testing prior to resection, and all participants demonstrated the predicted pattern of lateralization, so to the extent possible, our comparison groups were chosen to represent typical left- and right-hippocampal functions.

Bilingualism is another factor which may affect neuropsychological outcomes. Although research on the relationship between bilingualism and cognitive output is rather limited, some studies have demonstrated that variables such as age at acquisition of the second language (e.g., Hernandez & Li, 2007) and attained proficiency of the second language (e.g., Perani et al., 1998) may result in differences in neuropsychological performance. Other research has shown that bilingualism selectively affects semantic

verbal fluency (e.g, animal naming) but not phonemic fluency, free-form fluency, or sentence repetition tasks, and that these effects are more pronounced in groups with earlier age of acquisition of the second language (Rosselli et al., 2000). In the current study, participants were asked whether they were bilingual, and if so, at what age they learned English proficiently, in order to provide some measure of control for bilingualism when analyzing data, particularly for verbal measures. However, it may have been more informative to have conceptualized bilingualism as a continuous rather than dichotomous variable, so that potential moderating or mediating variables such as age of acquisition and attained proficiency could have been investigated.

Other factors which may have had an effect on the results of the current study include psychometric properties of the test instruments themselves, such as characteristics of the normative sample, kurtosis and skew of the distribution of the normative scores, measurement error, and the presence of ceiling or floor effects. Neuropsychological assessment utilizes a comparison model in which an individual's performance is compared to a normative sample; however, every neuropsychological test is normed on a different sample of the general population, making generalization to the entire population difficult. In addition, there are differences in the number and type of dynamic demographic variables included in normative information for individual comparison (i.e., whereas one test may include a set of norms based on age, gender, and education, others may only include age and specify that the normative sample included men and women with a certain educational level), so that an individual may be compared to quite variable normative samples to derive his or her standardized scores. This complicates the characterization of overall performance, or in the case of the present

study, may complicate the creation of composite scores based on data derived from differing normative samples. Characteristics of the distribution of the normative sample are also important to consider: whether the distribution is truly normal, or whether it has a positive or negative skew or kurtosis, affects the mean and standard deviation of the sample. As these are the most commonly used summary statistics when deriving normative data and level of individual performance, normality in the distribution is ideal. Floor and ceiling effects are often the source of positive and negative skew (e.g., in a sample in which most participants performed at perfect or near-perfect levels, there would be few low scores and an asymmetrical distribution of high scores, resulting in a negatively skewed distribution), and the decrease in variance of scores in the normative sample can result in somewhat biased standardized scores when applied in neuropsychological assessment. In addition, it is important to consider the reliability and measurement error of a test when deriving normative data. Rather than representing actual performance, test scores may best be conceptualized as representing an estimate of function with a specified degree of variance, or error: the lower the degree of measurement error, the more reliable the measurement in the general population and the more confidence in the validity of individual scores (Brooks, Strauss, Sherman, Iverson, & Slick, 2009).

In the current study, the psychometric characteristics of the measures have been well documented, and tests were chosen as much for their reported reliability as for the functions which they measure. In addition, by utilizing a multiple-methods design in which composite factor scores could be created, we can consider these values as trends rather than absolute values and make reasonable conclusions regarding the data.

Nevertheless, examination of the characteristics of the distributions of the composite factors in this study revealed several deviations from normality. The Verbal Memory, Non-Verbal Memory, Motor, Working Memory, and Executive Attention composites were negatively skewed, while the Language composite was positively skewed. The Visuospatial and Processing Speed composites were quite close to normal (with skewness statistics of 0.025 and 0.081, respectively). Regarding kurtosis, the Executive Attention composite was highly leptokurtic, while all other factors were platykurtic (no composite had a kurtosis statistic which approached 3.0, indicating normal peakedness). Thus, it may have been useful to apply a different set of statistical analyses to these composite scores, or to transform the variables statistically so that they more closely approximated a normal distribution.

One limitation of the present study was its small sample size, particularly in the schizophrenia and right TLR groups. Statistical analyses based on small sample sizes and unequal cell sizes can be problematic and it is likely that given a larger sample size and more evenly distributed group numbers, more reliable and significant results would have emerged, particularly given the high number of measures with trends in the expected direction (i.e., *p*-values between 0.05 and 0.1 or which did not meet post-hoc Bonferroni-corrected levels). In addition, data was missing for a small subset of participants, particularly in the right TLR group (e.g., SES, CPT-2), such that some analyses were based on even smaller sample sizes. Furthermore, small sample size results in reduced power to determine whether a difference exists between groups. For example, a large effect size (d = .64) would be necessary to detect a difference with 80% power between the schizophrenia and left TLR groups in the current study, based on sample sizes of 8

schizophrenia and 13 left TLR participants. In all likelihood, the actual effect size for the variables examined in the current study may be lower (particularly between schizophrenia and TLR groups, but perhaps less so between patient and control groups), thus concluding that no significant differences exist between schizophrenia and left TLR groups on memory and other neuropsychological domains may be premature. Likewise, an even larger effect size (d = .75) would be necessary to conclude with 80% power that a significant difference exists between the schizophrenia and right TLR groups, based on our sample sizes of 8 participants per group. Nevertheless, despite limited statistical power, significant differences on multiple variables did emerge between groups in the present study, suggesting that these variables may be useful in future research to further delineate the patterns of neuropsychological deficits in schizophrenia and TLR groups.

A second limitation, related to small sample size, is that we were unable to evaluate the influence of schizophrenia subtype (e.g., paranoid, disorganized, etc.) on cognitive outcome measures. Previous research has shown that, for example, although global indices of verbal memory and executive functioning in patients with paranoid schizophrenia are impaired in comparison to a normal control group, these deficits are not as pronounced as they are in patients with disorganized or undifferentiated schizophrenia (Bornstein, Nasrallah, Olson, Coffman, & Schwarzkopf, 1990). It is possible that performance on measures of verbal and nonverbal memory for different types of information, for example, rote memorization of semantically-unrelated words versus recall of contextual verbal information, may be differentially affected in schizophrenia subtypes as well, and would likely be more reliably examined in more homogenous subject populations. In addition, it should be noted that while significant differences

between the schizophrenia group and the healthy control group in our sample did emerge, the average standardized scores on most variables were not within what is typically considered a clinically significant range of impairment. It is possible that with a larger sample comprised of individuals with different subtypes of schizophrenia, patterns of memory performance specific to each subtype, with greater degrees of impairment in those groups with disorganized or undifferentiated subtypes, might emerge which would further supplement the existing literature on verbal memory in schizophrenia.

Furthermore, it should be noted that the age of onset of seizure activity in the left and right TLR groups in the current study was quite variable, ranging from infancy to 29 years of age. Previous research has demonstrated that age of seizure onset is correlated with hippocampal injury (i.e., younger age of onset results in greater hippocampal sclerosis), which is in turn related to memory functioning post-TLR (i.e., pre-TLR sclerosis is associated with equal or improved memory performance post-TLR, versus decreased memory performance in patients without medial temporal sclerosis; e.g., Bell & Davies, 1998; Davies et al. 1996; Hermann et al., 1995). The wide range of seizure onset age in the present study may have resulted in a mixed-outcome group of TLR patients, thus possibly obscuring potential differences.

In conclusion, the present study demonstrated that cognitive profiles in schizophrenia, involving memory alone and in conjunction with other neuropsychological domains, are highly complex and may best be represented by an interactive model rather than a simple model of hemispheric impairment such as that theorized to exist in temporal lobe epilepsy. These results seem to warrant future research to further explore the contributory role of overall attentional processing skills and general language ability

to impairments in verbal and non-verbal memory in schizophrenia, as well as the complicated relationship of frontal and temporal lobe structures and their interconnections to neurocognitive functioning in schizophrenia.

Appendices

Appendix A. Demographic Questionnaire

Demographic Questionnaire: "Assessment of Lateralized Hippocampal Function" & "Hippocampal Dependence of P50 Sensory Gating"

1. Study ID: _____

2. Date: _____

3. Study Group: SCZ LTLR RTLR NC

4. Gender: M F

5. Age: _____

6. DOB: _____

7. Ethnicity: _____

8. Education: _____

9. 1st Lang: English Other _____

Appendix B. Hollingshead Index of Social Position Scale (HISP)

Hollingshead Index of Position: Socioeconomic Status

Education Scale (Weighted by 4)	Subject	Mother	Father
Professional training (>16 years)	1	1	1
College graduate (16 years)	2	2	2
Some college (13-15 years)	3	3	3
High school graduate (12 years)	4	4	4
10-11 years of school	5	5	5
7-9 years of school	6	6	6
Under 7 years of school	7	7	7
TOTALS			

	Subject	Mother	Father
Occupational Scale (Weighted by 7)			
Higher executives, proprietors of large concerns and major professionals	1	1	1
Business managers, medium-sized business and lesser professionals	2	2	2
Administrative personnel, small independent business, minor professional	3	3	3
Clerical and sales workers, technicians, owner of little business	4	4	4
Skilled manual employees	5	5	5
Machine operators and semi-skilled employees	6	6	6
Unskilled employees	7	7	7
Housewives and students	8	8	8
TOTALS			

GRAND TOTALS			

Appendix C. Beck Depression Inventory, Second Edition (BDI-II)

BDI-II

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0. I do not feel sad.
1. I feel sad much of the time.
2. I am sad all the time.
3. I am so sad or unhappy that I can't stand it.

2. Pessimism

0. I am not discouraged about my future.
1. I feel more discouraged about my future than I used to be.
2. I do not expect things to work out for me.
3. I feel my future is hopeless and will only get worse.

3. Past Failure

0. I do not feel like a failure.
1. I have failed more than I should have.
2. As I look back, I see a lot of failures.
3. I feel I am a total failure as a person.

4. Loss of Pleasure

0. I get as much pleasure as I ever did from the things I enjoy.
1. I don't enjoy things as much as I used to.
2. I get very little pleasure from the things I used to enjoy.
3. I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0. I don't feel particularly guilty.
1. I feel guilty over many things I have done or should have done.
2. I feel quite guilty most of the time.
3. I feel guilty all of the time.

6. Punishment Feelings

0. I don't feel I am being punished.
1. I feel I may be punished.
2. I expect to be punished.
3. I feel I am being punished.

7. Self-Dislike

0. I feel the same about myself as ever.
1. I have lost confidence in myself.
2. I am disappointed in myself.
3. I dislike myself.

8. Self-Criticalness

0. I don't criticize or blame myself more than usual.
1. I am more critical of myself than I used to be.
2. I criticize myself for all my faults.
3. I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0. I don't have any thoughts of killing myself.
1. I have thoughts of killing myself, but I would not carry them out.
2. I would like to kill myself.
3. I would kill myself if I had the chance.

10. Crying

0. I don't cry any more than I used to.
1. I cry more than I used to.
2. I cry over every little thing.
3. I feel like crying, but I can't.

11. Agitation

0. I am no more restless or wound up than usual.
1. I feel more restless or wound up than usual.
2. I am so restless or agitated that it's hard to stay still.
3. I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0. I have not lost interest in other people or activities.
1. I am less interested in other people or things than before.
2. I have lost most of my interest in other people or things.
3. It's hard to get interested in anything.

13. Indecisiveness

0. I make decisions about as well as ever.
1. I find it more difficult to make decisions than usual.
2. I have much greater difficulty in making decisions than I used to.
3. I have trouble making any decisions.

14. Worthlessness

0. I do not feel I am worthless.
1. I don't consider myself as worthwhile and useful as I used to.
2. I feel more worthless as compared to other people.
3. I feel utterly worthless.

15. Loss of Energy

0. I have as much energy as ever.
1. I have less energy than I used to have.
2. I don't have enough energy to do very much.
3. I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0. I have not experienced any change in my sleeping pattern.
1a. I sleep somewhat more than usual.
1b. I sleep somewhat less than usual.
2a. I sleep a lot more than usual.
2b. I sleep a lot less than usual.
3a. I sleep most of the day.
3b. I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

0. I am no more irritable than usual.
1. I am more irritable than usual.
2. I am much more irritable than usual.
3. I am irritable all the time.

18. Changes in Appetite

0. I have not experienced any change in my appetite.
1a. My appetite is somewhat less than usual.
1b. My appetite is somewhat greater than usual.
2a. My appetite is much less than before.
2b. My appetite is much greater than usual.
3a. I have no appetite at all.
3b. I crave food all the time.

19. Concentration Difficulty

0. I can concentrate as well as ever.
1. I can't concentrate as well as usual.
2. It's hard to keep my mind on anything for very long.
3. I find I can't concentrate on anything.

20. Tiredness or Fatigue

0. I am no more tired or fatigued than usual.
1. I get more tired or fatigued more easily than usual.
2. I am too tired or fatigued to do a lot of the things I used to do.
3. I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0. I have not noticed any recent change in my interest in sex.
1. I am less interested in sex than I used to be.
2. I am much less interested in sex now.
3. I have lost interest in sex completely.

Appendix D. Magical Ideation Scale (MIS)

MIS

Please circle true (T) or false (F) for each question below.

1. **T F** Some people can make me aware of them just by thinking about me.
2. **T F** I have had the momentary feeling that I might not be human.
3. **T F** I have sometimes been fearful of stepping on sidewalk cracks.
4. **T F** I think I could learn to read other's minds if I wanted to.
5. **T F** Horoscopes are right too often for it to be a coincidence.
6. **T F** Things sometimes seem to be in different places when I get home, even though no one has been there.
7. **T F** Numbers like 13 and 7 have no special powers.
8. **T F** I have occasionally had the silly feeling that a TV or radio broadcaster knew I was listening to him.
9. **T F** I have worried that people on other planets may be influencing what happens on earth.
10. **T F** The government refuses to tell us the truth about flying saucers.
11. **T F** I have felt that there were messages for me in the way things were arranged, like in a store window.
12. **T F** I have never doubted that my dreams are the products of my own mind.
13. **T F** Good luck charms don't work.
14. **T F** I have noticed sounds on my records that are not there at other times.
15. **T F** The hand motions that strangers make seem to influence me at times.
16. **T F** I almost never dream about things before they happen.
17. **T F** I have had the momentary feeling that someone's place has been taken by a look-alike.
18. **T F** It is not possible to harm others merely by thinking bad thoughts about them.
19. **T F** I have sometimes sensed an evil presence around me, although I could not see it.
20. **T F** I sometimes have a feeling of gaining or losing energy when certain people look at me or touch me.

21. **T F** I have sometimes had the passing thought that strangers are in love with me.
22. **T F** I have never had the feeling that certain thoughts of mine really belonged to someone else.
23. **T F** When introduced to strangers, I rarely wonder whether I have known them before.
24. **T F** If reincarnation were true, it would explain some unusual experiences I have had.
25. **T F** People often behave so strangely that one wonders if they are part of an experiment.
26. **T F** At times I perform certain little rituals to ward off negative influences.
27. **T F** I have felt that I might cause something to happen just by thinking too much about it.
28. **T F** I have wondered whether the spirits of the dead can influence the living.
29. **T F** At times I have felt that a professor's lecture was meant especially for me.
30. **T F** I have sometimes felt that strangers were reading my mind.

Appendix E. Revised Social Anhedonia Scale (RSAS)

RSAS

Listed below are a series of statements a person might use to describe his/her attitudes, feelings, interests, and other characteristics. Read each statement and decide how well it describes you. If the statement is TRUE or MOSTLY TRUE, circle "T" in front of that item. If it is FALSE or MOSTLY FALSE, circle "F". There are no right or wrong answers, and no trick questions. Please answer every statement, even if you are not completely sure of the answer.

1. **T F** Having close friends is not as important as many people say.
2. **T F** I attach very little importance to having close friends.
3. **T F** I prefer watching television to going out with other people.
4. **T F** A car ride is much more enjoyable if someone is with me.
5. **T F** I like to make long distance phone calls to friends and relatives.
6. **T F** Playing with children is a real chore.
7. **T F** I have always enjoyed looking at photographs of friends.
8. **T F** Although there are things that I enjoy doing by myself, I usually seem to have more fun when I do things with other people.
9. **T F** I sometimes become deeply attached to people I spend a lot of time with.
10. **T F** People sometimes think that I am shy when I really just want to be left alone.
11. **T F** When things are going really good for my close friends, it makes me feel good too.
12. **T F** When someone close to me is depressed, it brings me down also.
13. **T F** My emotional responses seem very different from those of other people.
14. **T F** When I am home alone, I often resent people telephoning me or knocking on my door.
15. **T F** Just being with friends can make me feel really good.
16. **T F** When things are bothering me, I like to talk to other people about it.
17. **T F** I prefer hobbies and leisure activities that do not involve other people.
18. **T F** It's fun to sing with other people.
19. **T F** Knowing that I have friends who care about me gives me a sense of security.
20. **T F** When I move to a new city, I feel a strong need to make new friends.

21. **T F** People are usually better off if they stay aloof from emotional involvements with most others.
22. **T F** Although I know I should have affection for certain people, I don't really feel it.
23. **T F** People often expect me to spend more talking with them than I would like.
24. **T F** I feel pleased and gratified as I learn more and more about the emotional life of my friends.
25. **T F** When others try to tell me about their problems and hang-ups, I usually listen with interest and attention.
26. **T F** I never had really close friends in high school.
27. **T F** I am usually content to just sit alone, thinking and daydreaming.
28. **T F** I'm much too independent to really get involved with other people.
29. **T F** There are few things more tiring than to have a long, personal discussion with someone.
30. **T F** It made me sad to see all my high school friends go their separate ways when high school was over.
31. **T F** I have often found it hard to resist talking to a good friend, even when I have other things to do.
32. **T F** Making new friends isn't worth the energy it takes.
33. **T F** There are things that are more important to me than privacy.
34. **T F** People who try to get to know me better usually give up after awhile.
35. **T F** I could be happy living all alone in a cabin in the woods or mountains.
36. **T F** If given the choice, I would much rather be with others than alone.
37. **T F** I find that people too often assume that their daily activities and opinions will be interesting.
38. **T F** I don't really feel very close to my friends.
39. **T F** My relationships with other people never get very intense.
40. **T F** In many ways, I prefer the company of pets to the company of people.

Appendix F. Waterloo Handedness Questionnaire (WHQ)

WATERLOO SCALE

Instructions: Answer each of the following questions as best you can. If you always use one hand to perform the described activity, circle RA or LA (for right always or left always). If you usually use one hand, circle RU or LU, as appropriate. If you use both hands equally often, circle EQ. Do not simply circle one answer for all questions, but imagine yourself performing each activity in turn, and then mark the appropriate answer. If necessary, stop and pantomime the activity.

1. Which hand do you use for writing?	LA	LU	EQ	RU	RA
2. In which hand would you hold a heavy object?	LA	LU	EQ	RU	RA
3. With which hand would you unscrew a tight jar lid?	LA	LU	EQ	RU	RA
4. In which hand do you hold your toothbrush?	LA	LU	EQ	RU	RA
5. With which hand would you pick up a penny off a desk?	LA	LU	EQ	RU	RA
6. In which hand would you hold a match to strike it?	LA	LU	EQ	RU	RA
7. With which arm do you throw a baseball?	LA	LU	EQ	RU	RA
8. With which hand would you pet a cat or dog?	LA	LU	EQ	RU	RA
9. Which had would you use to pick up a nut or washer?	LA	LU	EQ	RU	RA
10. Which hand do you consider the strongest?	LA	LU	EQ	RU	RA
11. Over which shoulder would you swing an axe?	LA	LU	EQ	RU	RA
12. With which hand would you pick up a comb?	LA	LU	EQ	RU	RA
13. With which hand would you wind a stopwatch?	LA	LU	EQ	RU	RA
14. With which hand would you pick up a bar?	LA	LU	EQ	RU	RA
15. With which hand would you pick up a piece of paper?	LA	LU	EQ	RU	RA
16. With which hand do you use a pair of tweezers?	LA	LU	EQ	RU	RA
17. With which hand would you throw a spear?	LA	LU	EQ	RU	RA
18. With which hand would you hold a cloth when dusting the furniture?	LA	LU	EQ	RU	RA

19. With which hand do you flip a coin?	LA	LU	EQ	RU	RA
20. In which hand would you hold a knife to cut bread?	LA	LU	EQ	RU	RA
21. With which hand do you use the eraser on the end of a pencil?	LA	LU	EQ	RU	RA
22. With which hand would you pick up a toothbrush?	LA	LU	EQ	RU	RA
23. With which hand would you hold a needle when sewing?	LA	LU	EQ	RU	RA
24. On which shoulder do you rest a baseball bat when batting?	LA	LU	EQ	RU	RA
25. In which hand would you carry a briefcase full of books?	LA	LU	EQ	RU	RA
26. With which hand would you pick up a jar?	LA	LU	EQ	RU	RA
27. With which hand do you hold a comb when combing your hair?	LA	LU	EQ	RU	RA
28. With which hand would you pick up a pen?	LA	LU	EQ	RU	RA
29. Which hand do you use to manipulate instruments such as tools?	LA	LU	EQ	RU	RA
30. Which hand would you use to put a nut or washer on a bolt?	LA	LU	EQ	RU	RA
31. With which hand would you pick up a baseball?	LA	LU	EQ	RU	RA
32. Which hand do you use to pick up small objects?	LA	LU	EQ	RU	RA

33. Is there any reason (e.g., injury) why you have changed your hand preference for any of the above activities? YES NO (circle one)

34. Have you been given special training or encouragement to use a particular hand for certain activities? YES NO (circle one)

If you answered YES for either Question 33 or 34, please explain:

_____

_____

_____

_____

Appendix G. Participant Compensation Form

PARTICIPANT COMPENSATION SIGNATURE FORM

Project Title: Assessment of Lateralized Hippocampal Function
Principal Investigator: Faith M. Hanlon, Ph.D.
Additional Investigators: Michael Weisend, Ph.D., Robert J. Thoma, Ph.D., Rex Jung, Ph.D., & S. Laura Lundy, M.S.

I, the undersigned, certify that I have been paid $50 for my participation in the neuropsychological testing session for this study.

_____
Print Name

_____ _____
Signature Date

SIGNATURE OF INVESTIGATOR
I certify that the participant has been paid in full.

_____ _____
Signature Date

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